Neural Cells, Grown in Labs, Raise Hopes for Brain Disease Cures

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May 30, 2000
By ANDREW POLLACK

Sylvia Elam saw the benefits of her operation as soon as she was wheeled into the recovery room and ate lunch. For the first time in years, she could taste the food.

After a stroke in 1993, Mrs. Elam, of Scottsdale, Ariz., lost most of the movement and sensation on her right side. But last year she became one of the first people in the world to have cells manufactured in a laboratory implanted into her brain. The implant enabled Mrs. Elam, now 66, to talk again without stammering, to throw a ball with her right arm, to walk somewhat without a cane and even to drive a car.

"It was absolutely beyond our wildest dreams," said Mrs. Elam's husband, Ira.

Not all cases have had such positive results, but hope is growing that **neural** cells implanted into the brain can replace damaged cells and restore functions lost to stroke, spinal cord injury or neurological diseases like Parkinson's and Alzheimer's, most of which have **no** effective treatments.

"It's almost like reseeding your lawn," said Dr. Evan Y. Snyder, a neurologist at Children's Hospital in Boston and at Harvard Medical School, who has successfully used the technique to treat rats with a disease similar to multiple sclerosis.

In Mrs. Elam's case, a few months after the operation she suffered setbacks as a result of a second, apparently unrelated, stroke.

The quest to restore the **neural** connections in the brain has been spurred by two recent scientific developments.

One was the isolation of so-called stem cells, the primordial cells from which all others evolve, that can potentially be made into **neural** cells for transplantation.

In addition, in tests conducted in animals, the cells have had the ability to migrate through the brain to where they are needed to repair damage.

A second development was the discovery that adult brains continue to produce new cells, overturning conventional wisdom that brain cells are not replenished. This suggests some capacity for nervous system **regeneration**.

The discoveries have set off a race by companies hoping to develop cells to be sold for **neural** transplantation, part of the larger field of regenerative medicine. But harnessing such cells will require negotiating a minefield not only of technical challenges but of ethical ones, since most stem cells come from either embryos discarded by fertility clinics or aborted fetuses.

Some scientists and business executives worry that the **neural** implant field will repeat the history of gene therapy, which has gone through 10 years of largely dashed hopes, controversial clinical trials and burned investors, though there have been some recent signs of success.

"We would do well to learn the lesson from the troubled path of the gene therapy field: not to promise too much too early," wrote Anders Bjorklund and Olle Lindvall, Swedish scientists, in a commentary in the June issue of Nature Neuroscience.

They said they see signs of a rush toward "ill-founded clinical trials" without adequate scientific rationale.

Still, the two scientists have been implanting brain **tissue** from aborted human fetuses into the brains of people with Parkinson's disease, which causes a loss of motor skills, for almost a decade. In some patients the treatment has caused a slight improvement in motor control, which has lasted 5 to 10 years.

But such treatment, which has also been done in this country, requires several fetuses for each patient. Moral questions notwithstanding, there are simply not enough fetuses to treat this nation's million or more Parkinson's patients.

So scientists are searching for cells that can be mass produced -- "neurons in a bottle," said George W. Dunbar Jr., acting chief executive officer of StemCells Inc., in Sunnyvale, Calif., one of the companies pursuing the treatments.

The cells implanted in Mrs. Elam were supplied by Layton BioScience Inc., also of Sunnyvale, and derived from testicular cancer cells isolated from a patient in the 1970's. Scientists found, almost serendipitously, that when treated with chemicals called retinoids, some of the cells turned into **neural** cells. Six of the 12 stroke patients treated with the cells had some improvement in motor skills, said Dr. John Kondziolka, the University of Pittsburgh neurosurgeon who performed the operations.

Similar hints of success have been found in clinical trials run by Diacrin Inc. of Charlestown, Mass., the company furthest along in **neural** cell implants. It harvests brain cells from pig fetuses, which have been used to treat more than 20 Parkinson's patients and several with stroke, Huntington's disease and epilepsy.

But there are fears the cancer-derived cells could cause cancer and that cells from pigs could infect patients with animal viruses.

Diacrin recently suspended its trials on stroke victims after two of five patients suffered seizures, though the company does not think the pig cells were the cause. While Layton and Diacrin say their cells are safe, some experts think they will eventually be replaced by alternatives that are less

unappealing to patients.

That would mean human stem cells, which can be grown in great quantities. The greatest excitement revolves around so-called embryonic stem cells, which were first isolated in 1998 by Dr. James Thomson of the University of Wisconsin. These cells can turn into virtually any cell in the body -- including the liver, kidney, blood or heart, as well as neurons.

But such cells are at the center of an ethical controversy, with opponents saying it is immoral to use embryos for medical purposes.

By law, federal money cannot be used for research involving the destruction of embryos.

The National Institutes of Health has proposed new guidelines to allow scientists receiving its money to work with the cells, provided that the cells are created with private money.

Senators Arlen Specter, Republican of Pennsylvania, and Tom Harkin, Democrat of Iowa, have proposed a bill that would ease the restrictions. But abortion opponents remain opposed to any such relaxation.

The research ban does not affect scientists with corporate financing, which has allowed companies to dominate the field.

Geron Corporation of Menlo Park, Calif., which financed the work at Wisconsin, has commercial rights to the embryonic stem cells.

It also has the patent rights to a similar type of primordial cell isolated by Dr. John Gearhart of Johns Hopkins University, also with Geron financing.

Other companies, looking to sidestep both Geron's patents and the ethical issues surrounding embryonic cells, are using so-called **neural** stem cells on which they have obtained patents. These are less versatile than embryonic stem cells. They can turn into different types of **neural** cells but probably not into others, like kidney or liver cells.

But those working with **neural** stem cells say that might even be an advantage for treating a neurological disease. Embryonic stem cells "turn into bone cells and knee cells," said I. Richard Garr, president and chief executive of NeuralStem Biopharmaceuticals Ltd. of College Park, Md.

"You can't put them in a person's head without being 100 percent sure they won't turn into these other things."

Dr. Thomas B. Okarma, president and chief executive of Geron, countered that embryonic cells could more easily be multiplied and made to live forever than the **neural** stem cells, providing an endless supply. "The more upstream you start, the more total control," he said.

In **neural** stem cells, NeuralStem is competing with StemCells Inc., a publicly traded company that was **known** as CytoTherapeutics Inc. until it abandoned its previous business to focus on stem cells. Layton, which made the cells used on Mrs. Elam, has now also moved into **neural** stem cells by obtaining from Children's Hospital in Boston a license for a line of cells developed by Dr. Snyder.

The other companies also have strong scientific credentials. NeuralStem was founded by scientists from the National Institutes of Health laboratory of Dr. Ronald McKay, a pioneer in **neural** stem cells.

StemCells counts among its scientific advisers Dr. Irving L. Weissman, a stem cell expert at Stanford, and Dr. Fred H. Gage of the Salk Institute for Biological Sciences, who made some of the crucial discoveries that the adult brain can grow new cells.

Other companies in the emerging field include ReNeuron Ltd. in London and Neuronyx of Malvern, Pa., which is headed by Hubert Schoemaker, the former chief executive of Centocor, a leading biotechnology company now owned by Johnson & Johnson.

The **neural** stem cells are not free of ethical controversy, since they generally come from fetuses. But the companies say that since they can multiply the cells in the laboratory, they might need only a single fetus to supply hundreds of patients, if not the entire world demand.

"If we had to go back to human fetal material on a continuing basis, that would be a concern," said Gary L. Snabel, president and chief executive of Layton. But with only a few fetuses needed for all time, "most people would say that's not an unreasonable strategy."

The recent discoveries that adult brains still contain some stem cells makes it possible to derive such cells from adults, which would remove the ethical questions. But the scientists say the fetal cells are easier to obtain and easier to grow and that adult stem cells might lack the resiliency of the embryonic or fetal ones.

There are still many technical problems to overcome with both **neural** stem cells and embryonic stem cells, and it could be several years before clinical trials begin.

The biggest challenge is trying to get the stem cells to reliably turn into a single desired type of cell, which is usually done by exposing the cells to certain growth factors or implanting particular genes in them. This cannot be done yet for embryonic stem cells, though there has been progress.

Dr. McKay of the health institutes has turned mouse embryonic stem cells into **neural** cells that produce dopamine, the chemical lacking in patients with Parkinson's.

Another approach is to use drugs to try to stimulate the brain to grow its own new cells.

Harry M. Tracy, publisher of Neuroinvestment, an investment newsletter in Rye, N.H., that follows the neurological medicine companies, said some of the drugs might reach the market before stem cell implants. Still, he said, a combination of both approaches would probably be needed.

Rebuilding With Stem Cells

Stem cells, the master cells from which all other cells in the body develop, might be used to replenish many other tissues.

Companies are trying to harness the cells to rebuild hearts, bone, blood and other tissues, part of a field coming to be called regenerative medicine.

At the Geron Corporation of Menlo Park, Calif., scientists have already turned embryonic stem cells into heart muscle cells that spontaneously beat in the test tube. Studies in mice have shown these cells integrate into the heart.

Such stem cell therapy might be used to rebuild hearts after a heart attack, since heart muscles do not regenerate after being killed.

Osiris Therapeutics of Baltimore is starting clinical trials to see if stem cells can be used to regrow bone. It is using mesynchymal stem cells, which turn into the body's connective **tissue**, like bones, cartilage, tendons and bone marrow.

The biggest existing use of stem cells is for bone marrow transplants to replenish the body's immune system. This works because the marrow is rich in hematopoietic stem cells, which turn into blood cells.

Some companies are trying to make a business of technology that can be used in stem cell therapy. Aastrom Biosciences of Ann Arbor, Mich., has a device that can multiply cells, including stem cells.

Nexell Therapeutics of Irvine, Calif., also has techniques for separating and growing cells. Its device was used to multiply cells used recently in what is considered the world's first gene therapy success: French scientists' treatment of three girls with a rare immune disease.

Ariad Pharmaceuticals of Cambridge, Mass., recently published a scientific paper about technology it developed that could help control the growth and differentiation of stem cells.

Other uses of stem cells could provide income before cell transplants become feasible. Geron expects its first stem cell profits to come from making liver cells that pharmaceutical companies can use to test how well a **drug** is metabolized by the liver and whether the **drug** causes liver toxicity. NeuralStem Biopharmaceuticals has signed an agreement with Gene Logic, a genomics company, to use the stem cells to help define the functions of genes.

--ANDREW POLLACK

Brain Neurology: The Neuron

The Cell

Nervous tissue is composed of specialized working cells called **neurons**. The neuron is the basic operating unit of the nervous system. **Neurons** conduct nerve impulses that are formed by tiny electrical charges passing along the membranes of the **neurons**. This allows information to be initiated, sent, received, and processed. **Neurons** send information to make muscles move (motor **neurons**) and receive input from sensory organs and muscles. Basically, **neurons** do one of two things: they transmit the electrical impulse or they don't.

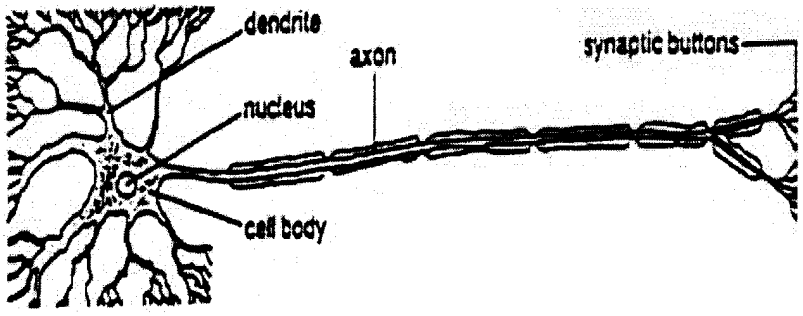
Neurons do not reproduce themselves after reaching maturity. If a neuron dies, it is not replaced. However, connections between various intact **neurons** can grow and be altered through growth and after brain injury.

The **neurons** of the cerebral cortex may have as many as 20,000 connections to other **neurons** in order to form the basis of complex information processing systems, i.e., thinking. All **neurons** are composed of three basic parts: the **DENDRITE**, CELL BODY and AXON.

Dendrite: The **dendrite** is thin fiber projecting from the neuron whose purpose is to receive nerve impulses from other **neurons**. The **dendrite** performs the "input" functions of the neuron. A neuron can have from one to several thousand dendrites. The **dendrite** will either "fire" and transmit electrical impulses to the neuron or remain dormant.

Cell Body: The cell body is the part of the neuron that performs the metabolic activity of the cell. It contains the nucleus and other organs necessary for cell life. If this part of the cell is damaged, cell death usually results.

Axon: The axon is usually the longest fiber or fibers projecting from the cell body. The axon directs electrical information away from the cell, performing the "output" function for the neuron. Axons can be very long and are often severely damaged in traumatic brain injury, resulting in cell death.



The Space Between The Cells

The billions of **neurons** in the brain are not directly connected to each other. There are tiny spaces between their fibers (dendrites and axons) called SYNAPSES. **Neurons** are able to communicate with each other by sending chemicals called NEUROTRANSMITTERS across a space between each neuron at the SYNAPSE. These neurotransmitter chemicals either excite the next neuron to continue sending the electric charge or inhibit it from sending the charge.

Synapse: The synapse is the tiny space that is usually between the axon of one neuron and the **dendrite** of another neuron. The two **neurons** communicate across this space. At the end of the axon sending the impulse to the synapse, the electrical charge releases specialized chemicals into the space of the synapse· These chemicals, called NEUROTRANSMITTERS, travel across to the end of the **dendrite** of the adjacent neuron, influencing the next neuron to either "fire" (begin transmitting the electrical charge) or remain dormant.

Neurotransmitters: Neurotransmitters are the chemicals released by the "transmitting" axon of one neuron into the synapse space in order to excite or inhibit the electrical activity of the next neuron. The neurotransmitters travel across the synapse to the dendrites of the "receiving" neuron. The brain has a number of different specialized neurotransmitters that are used in different regions of the brain. Common neurotransmitters are adrenalin, acetylcholine, and dopamine.

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Research Shows Bone Marrow Stem Cells Able to Become Brain Cells
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Using a combination of growth factors and other nutrients, scientists at Jefferson Medical College have shown the ability to convert adult human **bone marrow stem** cells into adult brain cells during laboratory tests. While it's early in the research, the results suggest **stem** cells may have potential use in someday treating neurodegenerative diseases such as Alzheimer's and Parkinson's disease.

Dr. Iacovitti, developmental biologist, Ph.D., professor of neurology at Jefferson Medical College of Thomas Jefferson University in Philadelphia, leads the research. She and her team used a cocktail of growth factors and nutrients on human **bone marrow stem** cells and found that only some cells converted to neurons; that is, they looked like neurons in that they developed "cellular processes." She recently reported her team's findings at the annual meeting of the Society for Neuroscience.

But by experimenting with different combinations of growth factors and nutrients, they eventually found a cocktail of reagents that converted 100 percent of cells within an hour - a stunning development that had never been shown before.

"It flew in the face of everything I knew from developmental biology," Dr. Iacovitti says. "We've identified factors that get 100 percent of adult human **bone marrow stem** cells converted to neurons very quickly." Not only do the converted cells look like neurons, she says, they contain **neuronal** proteins.

Human adult **bone marrow stem** cells, or pluripotent **stem** cells, normally give rise to human **bone**, muscle, cartilage, and fat cells. Embryonic **stem** cells, in contrast, can become any type of **cell**. The converted **stem** cells have **neuronal** markers and markers that are identified with subclasses of neurons.

"That's important because we've shown they can convert to specific classes of neurons. We have seen serotonin and GABA enzyme neurons. We want to get them to convert to dopamine neurons, which we haven't seen yet."

"The major advantage of using adult human **bone marrow stem** cells is that each person can be his own donor, meaning they can have an autologous graft of cells without

rejection," Dr. Iacovitti said. "The hope is that we won't have to use embryonic **stem** cells and aborted fetuses for **stem cell** lines."

There is one caveat, she notes. To date, the new neurons revert back to their original undifferentiated state in two to three days.

"The bigger problem to solve is how to keep them differentiated," Iacovitti said. A key, she says, may lie in understanding what occurs in the growth media in which the **stem** cells incubate for several days and into which they release certain growth factors.

If the "conditioned" growth media plays a role in the conversion to neurons, the researchers, "hope to find ways to remove the **stem** cells from the culture - which is difficult - and differentiate them into what we want." The next step, Iacovitti says, will be for her team to both better understand the **stem cell** conversion in the laboratory and to study the process in animals.

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Developmental Biology

Hematopoietic progenitors express neural genes

James Goolsby,[*,†] Marie C. Marty,[‡] Dafna Heletz,[*,†] Joshua Chiappelli,[*,†] Gerti Tashko,[*,†] Deborah Yarnell,[*,†] Paul S. Fishman,[*,†] Suhayl Dhib-Jalbut,[*,†] Christopher T. Bever, Jr.,[*,†] Bernard Pessac,[§] and David Trisler[*,†¶]

[*]Department of Neurology, University of Maryland School of Medicine, Bressler Research Building 12-041, 655 West Baltimore Street, Baltimore, MD 21201; and [†]Multiple Sclerosis Center of Excellence, Veterans Affairs Medical Center, Baltimore, MD 21201; and [‡]Centre National de la Recherche Scientifique, Unité Mixte de Recherche 8118, and [§]Unité de Formation et de Recherche Biomedicale des Saints-Pères, 45 Rue des Saints-Pères, 75006 Paris, France

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[¶] To whom correspondence should be addressed. E-mail: dtris001@umaryland.edu.

Abstract

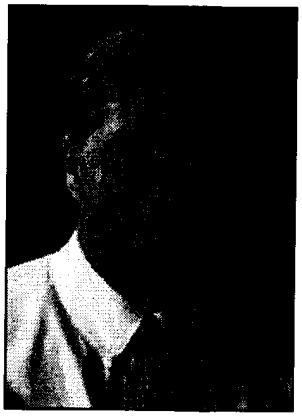
Bone marrow, or cells selected from bone marrow, were reported recently to give rise to cells with a neural phenotype after *in vitro* treatment with neural-inducing factors or after delivery into the brain. However, we showed previously that untreated bone marrow cells express products of the neural myelin basic protein gene, and we demonstrate here that a subset of *ex vivo* bone marrow cells expresses the neurogenic transcription factor Pax-6 as well as neuronal genes encoding neurofilament H, NeuN (neuronal nuclear protein), HuC/HuD (Hu-antigen C/Hu-antigen D), and GAD65 (glutamic acid decarboxylase 65), as well as the oligodendroglial gene encoding CNPase (2′,3′ cyclic nucleotide 3′-phosphohydrolase). In contrast, astroglial glial fibrillary acidic protein (GFAP) was not detected. These cells also were $CD34^+$, a marker of hematopoietic stem cells. Cultures of these highly proliferative $CD34^+$ cells, derived from adult mouse bone marrow, uniformly displayed a phenotype comparable with that of hematopoietic progenitor cells ($CD45^+$, $CD34^+$, Sca-1^+, AA4.1^+, cKit$^+$, GATA-2^+, and LMO-2^+). The

neuronal and oligodendroglial genes expressed in *ex vivo* bone marrow also were expressed in all cultured $CD34^+$ cells, and GFAP was not observed. After $CD34^+$ cell transplantation into adult brain, neuronal or oligodendroglial markers segregated into distinct nonoverlapping cell populations, whereas astroglial GFAP appeared, in the absence of other neural markers, in a separate set of implanted cells. Thus, neuronal and oligodendroglial gene products are present in a subset of bone marrow cells, and the expression of these genes can be regulated in brain. The fact that these $CD34^+$ cells also express transcription factors (Rex-1 and Oct-4) that are found in early development elicits the hypothesis that they may be pluripotent embryonic-like stem cells.

The University of Michigan Medical School Department of

CELL & DEVELOPMENTAL BIOLOG

Sean J. Morrison, Ph.D.
*Assistant Professor of **Cell** & Developmental Biology*
Assistant Professor of Internal Medicine (Molecular Medicine and Genetics)
Assistant Investigator, Howard Hughes Medical Institute
3215 CCGC
(734) 647-6261
Email: seanjm@umich.edu



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Stem cells are self-renewing multipotent progenitors that give rise to all of the other cells in particular tissues. For example, **hematopoietic** stem cells (HSCs) are the rare cells in bone marrow that give rise to all blood and immune system cells. **Neural** crest stem cells give rise to a number of different tissues including the peripheral nervous system. Given their seminal roles in development and regeneration, stem cells define the nexus of important questions in both developmental biology and clinical applications. We study stem **cell** biology using hematopoiesis and **neural** development as model systems. The next challenge in stem **cell** biology will be to integrate what we know about stem cells in different tissues in order to understand common mechanisms of regulation and distinctions that permit tissue-appropriate development. Our work on stem **cell** regulation encompasses both molecular and cellular questions, from the role of transcription factors in **cell** fate determination to changes in the properties of stem cells during ontogeny.

Conserved genetic programs may regulate stem **cell** self-renewal in the **hematopoietic** and nervous systems. We study the regulation of self-renewal in both HSCs and **neural** crest stem cells (NCSCs). We have complementary tools available in the two systems given our ability to isolate HSCs with successive reductions in self-renewal potential in vivo and our ability to purify NCSCs by flow-cytometry and study their self-renewal in vitro. We have previously shown that telomerase and Ikaros may play roles in the self-renewal and differentiation of HSCs. To the extent that changes in telomerase and Ikaros expression have been implicated in tumorigenesis, genetic programs that regulate the self-renewal of stem cells may be inappropriately activated in cancer cells.

A distinction between the **hematopoietic** and nervous systems is the regional specialization that develops in the nervous system. This is at least partially driven by regulation at the level of stem cells and suggests aspects of regulation that do not exist in the **hematopoietic** system. Based on our recent finding that NCSCs persist into late gestation in peripheral nerves we will study whether similar or different types of stem cells persist in other regions of the developing nervous system. To what extent is **neural** diversity driven by the diversification of stem cells and how does this affect plasticity?

Representative Publications:

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2. Morrison, S.J., P.M. White, C. Zock, D.J. Anderson. 1999. Prospective identification, isolation by flow cytometry and in vivo self-renewal of multipotent mammalian **neural** crest stem cells. **Cell** 96:737-749.

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Nerve Regeneration

This website explores four biotechnological approaches to nerve regeneration: stem cell therapy, guidance channels, neurotrophic factors, and gene therapy.

What is the central nervous system?

At the core of the human nervous system, a control system of the body, is the central nervous system (CNS), which is composed of the brain and spinal cord. Using electrical signals that travel from the CNS through the peripheral nervous system (PNS), the brain controls effector cells, which carry out the physiological responses "requested" by the brain. Thus, the nervous system is a "wired" communication system of the body.

Anatomically, the fundamental cell of the brain is the neuron, which consists of a cell body, branch-like extensions off the cell body called dendrites, and at least one longer extension off the cell body called an axon. The dendrites conduct signals from their tips toward the neuron cell body whereas the axon carries messages away from the cell body toward the terminal end of the axon. The neuron communicates with other cells, such as effector cells, through the distal tips of the axon.

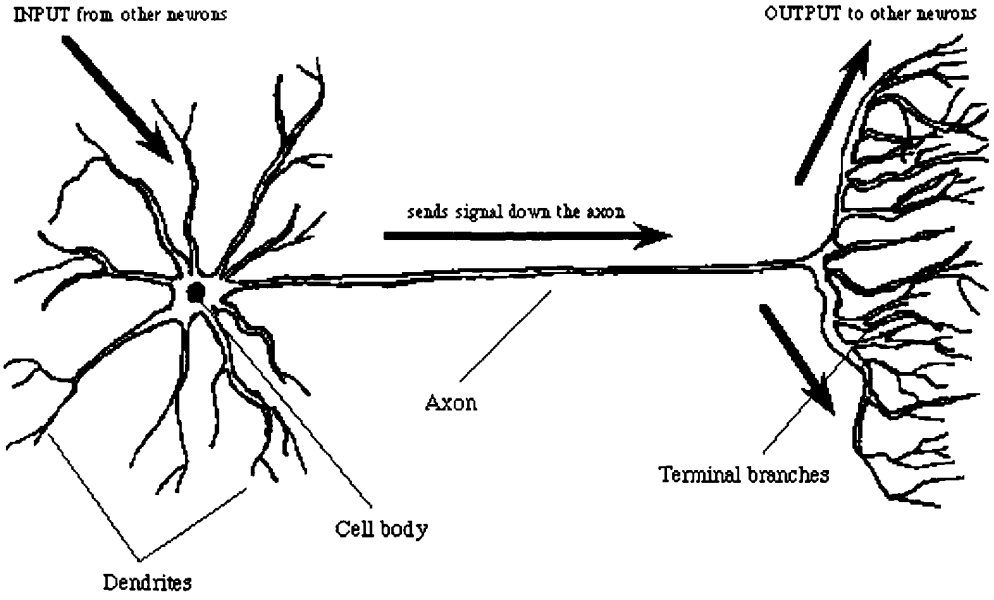

Diagram of a neuron.
Source: http://www.ccs.neu.edu/groups/honors-program/freshsem/19951996/cloder/neuron.html

Nerves are bundles of axons from different neurons that carry signals in the same direction; nerves are the essential intermediary connecting the brain to effector cells. Thus, if nerves are severely damaged, the signal between the cell body and effector cells is interrupted, and neurons are unable to convey effective "requests," such as a muscle movement. This is similar to cutting an electrical cord connecting a lamp to an outlet.

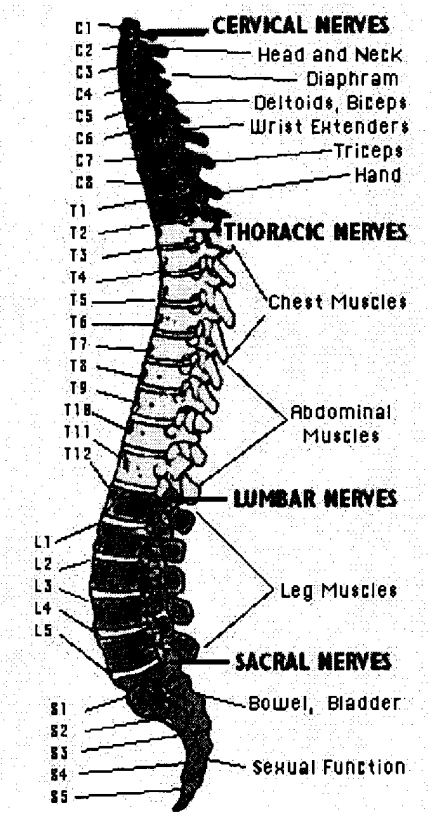

Diagram illustrating the spinal nerves and their function
Source: http://www.spinalinjury.net/html/_spinal_cord_101.html

What damages nerves?

Nerves can be damaged either through trauma or disease. **Nerve** trauma may be incurred through motor vehicle accidents, severe falls, lacerations, and typing. Traumatic **nerve** injury, such as carpal tunnel syndrome, is caused by the compression of nerves. Other trauma, such as falls and motor vehicle accidents, may lead to the severance of nerves. Diseases that damage nerves include multiple sclerosis, diabetes, spina bifida, and polio. Multiple sclerosis, for example, causes the breakdown of the insulating myelin surrounding axons.

The most dramatic and serious **nerve** damage occurs to the spinal cord. Damage to the lower spinal column may lead to paraplegia, paralysis of the lower extremities, and damage to the upper spinal column may lead to quadriplegia, paralysis of all four extremities. The incidence of spinal cord injury in the US is 11,000 per year and the prevalence is 250,000 to 400,000. The cost to support a patient with a spinal cord injury through his or her lifetime is estimated to cost between $400,000 to $2.1 million depending on the severity of injury.

Actor Christopher Reeve's well-publicized horse riding accident in 1995, which led to his becoming quadriplegic, has recently brought national attention to the debilitating effects of spinal cord injury. Following his accident, The Christopher Reeve Paralysis Foundation was established to fund research for paralysis.

Why can't the CNS heal damaged nerves itself?

Unlike a cut that heals, the central nervous system has limited ability to fix its damaged nerves, in contrast to the peripheral nervous system. When parts of the central nervous system are critically injured, the CNS cannot generate new neurons nor regenerate new axons of previously severed neurons. Severed CNS tips initially try to grow, but eventually abort and ultimately completely fail to regenerate. A look into this mechanism will reveal much about how and why the CNS works the way it does.

Remarkably, almost 90% of cells in the CNS are not even neurons. Rather they are glial cells, which play an important role in supporting neurons both physically and metabolically. They maintain the extracellular environment to best suit and nourish neighboring neurons. The CNS and PNS have two distinct types of glial cells, and they are what accounts for the discrepancy in regenerative ability.

In the PNS, the glial cells are Schwann cells that don't inhibit axon **regeneration**. Their sole function here is to produce myelin to facilitate more effective transportation of neurotransmitters.

In the CNS, there seem to be two "glial culprits" that inhibit axon **regeneration**. These are oligodendrocytes and astrocytes. Both play key roles in CNS support and metabolism. It is logical to ask hear, "why on earth would the body ever want to inhibit regenerative ability?" The body has a good answer.

This growth-inhibiting action helps enormously in stabilizing the outrageously complex CNS. This highly organized complex must be maintained, and the growth-inhibitors provide a cellular 'scaffold' so that neurons only sprout to where they are intended. The inhibitors effectively lock the connections into place. Without these proteins, the CNS may not be able to organize itself and work properly. The tradeoff, though, is that the CNS has no ability to regenerate itself in the event of injury. Since the PNS is capable of **regeneration**, it is evident that cellular mechanisms exist to promote **nerve regeneration**.

How can nerve damage be fixed?

As of now, there is no **cure** for **nerve** damage. To prevent secondary damage, steroids such as methylprednisolone can reduce the swelling that results from spinal cord injury, and Sygen, a recently discovered drug, appears to reduce the loss of **nerve** function.

However, recent biotechnology holds promise for **nerve regeneration**. This commercial (requires QuikTime, source: http://www.adcritic.com) by Nuveen Investments shows Christopher Reeve walking, an optimistic and plausible outlook. Explored here are four ways scientists are trying to regenerate nerves in vivo:

1) Guidance Channels
2) Stem Cells
3) Growth Factors
4) Gene Therapy

Regeneration Therapies

Please note: these are draft pages we put them together so we could collaborate more efficiently and we do invite suggestions from researchers.

1. Sub-Category Index

a. IN-1, the monoclonal antibody against neurite inhibitor factor (NIF) from Schwab
b. NT3 - neurotrophic growth factor
c. Anti-Mag - antibodies against myelin-associated glycoprotein
d. L1 - a cellular adhesion molecule
e. many others that have not yet tried in spinal cord injury models.
g. Scar Disrupters combined w/NGF

2. Regeneration: Introduction
by Dr. Wise Young, January 18,1996

Regeneration of the spinal cord has been the holy grail of neuroscientists for many years. At the turn of the century, the famous Spanish neuroanatomist Santiago Ramon y Cajal convinced the world

the brain and spinal cord are composed on specialized cells called neurons that contacted and communicated with each other through long processes called axons.

The spinal cord is composed of long tracts of axons that connect neurons in the brain and neurons in the spinal cord. Axons are covered with a white sheathing called myelin. Cajal noted that when he cut the spinal cord, the distal part of the axon would die while the proximal part tended to die back a short distance. Some of the axons tried to regrow but only for short distances and would stop. Based on these observations, most scientists concluded that the brain and spinal cord neurons cannot regenerate. However, axons in peripheral **nerve** will grow back if cut.

In the early 1980's, Albert Aguayo at the Montreal Institute of Neurology in Canada came to a different conclusion. He stuck peripheral nerves into the spinal cord and found that brain and spinal neurons will send axons into the peripheral nerves and these axons grew long distances. He suggested that there was something in brain that inhibited axonal growth. This stimulated an intense search for inhibitory substances in the spinal cord.

In 1987, the Swiss researcher Martin Schwab showed that myelin (the sheathing that covers axons in the central nervous system) contains a protein that blocks **regeneration**. He showed that axons will be grow in the presence of this protein. He subsequently developed an antibody to block the protein and found that this antibody allowed **regeneration** in the spinal cord. Reported in 1991, this was the first time a treatment was able to stimulate **regeneration** in the spinal cord. This discovery has led to an intense search for other potentially inhibiting factors. Several others have been reported, i.e. myelin-associated glycoprotein (MAG) and others.

In the meantime, other researchers, particularly the Hans Thoenen and Yves-Alain Barde in Germany, discovered that the brain and spinal cord produce growth factors that stimulated **nerve** growth. A family of these growth factors, called neurotrophins, have now been identified. One of these factors, NT-3, appeared to be particularly effective stimulating growth of spinal axons. In 1993, Schwab showed that a combination of the antibody (called IN-1) and a neurotrophic factor (called NT3) was better than either alone. In December 1996, Schwab published an important paper with Barbara Bregman, showing that IN1-NT3 treatment resulted in functional recovery.

Several laboratories have begun reporting that cellular adhesion molecules (CAM) play a major role in axonal growth. CAMs are molecules that are present on membrane surfaces and have long been believed to guide growing axons. However, Melitta Schachner in Switzerland showed that one CAM called L1 not only strongly stimulated axonal growth but appeared to do so despite the presence of the inhibiting glycoprotein described by Schwab.

Schachner proposed that L1 is the natural antagonist to growth inhibiting proteins of the central nervous system. Several observations strongly supported this proposal. First, wherever L1 is present, axonal growth occurs. For example, during embryonic development, when the spinal cord grew. Also, peripheral nerves express L1 and can regenerate. Second, L1 is absent in tissues that cannot regenerate. For example, L1 is largely absent from white matter in adult spinal cords. Third, when she genetically manipulated mouse to express L1 in the adult central nervous system. Seveal laboratories, including NYU, are actively pursuing this lead.

A large number of growth factors have been reported to stimulate neuronal growth, including fibroblast growth factor (FGF), brain-derived neurotrophic factor (BDNF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and others. None of these, however, have yet to be tested in standardized **animal** spinal cord injury models. Many other substances show promise in tissue culture studies have have not yet been tested in vivo. Finally, many laboratories have been studying implantation of fetal cells into the spinal cord but the political ramifications of **human** fetal cell transplants may interfere.

In summary, recent advances indicate that **regeneration** can occur in the spinal cord under the right circumstances. It is likely that the treatment will include not only a growth factor but a factor that antagonizes endogenous growth inhibitors in central nervous tissues. **Animal** studies are progressing and there is no dearth of factors and substances to test in the laboratory.

5. Human Trials

Depending on what the **animal** studies show, the first regenerative therapies for spinal cord injury are probably either IN1 or possibly L1, combined with NT3. IN1+NT3 is the only treatment has has so far been shown to result in functional recovery associated with **regeneration** in mammalian spinal cord. There are many issues to be settled, including the delivery vehicle, whether we would use genetically modified cells that secrete these factors or whether we would deliver the drug directly to the spinal cord through intrathecal catheters. Given the current state of funding and progress, perhaps the first regenerative therapies will go into clinical trial 4-8 years from now.

Background Treatments that regenerate the spinal cord include IN1 (the antibody that blocks inhibitory proteins in the spinal cord) and NT3 (neurotrophin-3, the growth factor shown to stimulate spinal axonal growth in rats). Swiss researcher Dr. Martin Schwab showed in 1987 that spinal white matter contains a protein that stops **regeneration**. Blockade of this protein with a monoclonal antibody resulted in the first demonstration of **regeneration** in mammals by 1991. In 1993, Schwab showed that a combination of the antibody (called IN-1) and a neurotrophic factor (called NT3) was better than either alone.

In January of 1996, Schwab published an important paper with Barbara Bregman, showing that IN1-NT3 treatment resulted in functional recovery. This discovery has led to an intense search for other potentially inhibiting factors. Several others have been reported, i.e. myelin-associated glycoprotein (MAG) and others.

In the meantime, several laboratories have begun reporting that cellular adhesion molecules (CAM) play a major role and are likely to be the natural antagonists to the growth inhibiting proteins of the central nervous system. In particular, Melitta Schachner has shown that a CAM by the name of L1 strongly stimulates **regeneration** in the central nervous system and L1 studies are now being carried out in spinal cord injury models in a number of laboratories, including NYU, Miami Project, UCSD, Case Western, and others.

Depending on what the **animal** studies show, we are hoping to start therapy with IN1 or L1, combined with NT3, sometime in 1998. We are still uncertain of the delivery vehicle, whether we would use genetically modified cells that secrete these factors or whether we would deliver the drug directly to the spinal cord through intrathecal catheters.

6. Funding Issues

Martin's antibody patent has been assigned to a company called Regeneron. Although Martin is working very hard on isolating the glycoprotein that is responsible for inhibiting **regeneration**, he has not yet been successful.

He has gone on to show that treatment with IN1 and NT3 combined does result in better restoration of locomotor function. After nearly a year of wrangling, his paper reporting this was accepted by Nature and will be published next month.

Unfortunately, Regeneron has indicated to me that they are not interested in and have no plans to invest in spinal cord injury therapies. They believe that the field is too small and risky to warrant the investment. I am hoping to convince Regeneron to license the treatment to us so that we can take it to clinical trial. The problem is money. No major pharmaceutical company is interested in investing the $50-$200 million necessary to take a treatment from laboratory to market, for spinal cord injury.

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Spinal Cord Injury Association

of Illinois

1032 S. LaGrange Road - LaGrange, Illinois 60525-2865 - (708) 352-6223 - Fax: (708) 352-9065

E-Mail: SCIInjury@aol.com

Spinal Cord Injury Treatment and Cure Research

When spinal cord injury (SCI) occurs, one of the most difficult issues to deal with is that there is no "cure" at the present time. One would think that with the explosion in scientific knowledge we hear of every day someone would find a cure for people with SCI. If we can achieve the impossible in other areas like transplanting entire organs and organ systems from one person to another and isolating human genes, why can't we figure out why the spinal cord does not repair itself and then do something to correct this biological problem? Compared to a lot of the scientific puzzles that have been solved, it shouldn't be all that difficult.

There are two separate issues involved in this assumption – is the scientific question, "Why won't the spinal cord regenerate" easy to answer? Secondly, what is being done to find a cure?

Let's look at these issues and put them into the context of what scientists have been doing about spinal cord injury over the past half century.

Before World War II, an injury to the spinal cord was considered to be a fatal condition. If one did not die as a direct result of the injury, he or she would probably dies within a few weeks or months from complications, such as kidney infection, respiratory problems, or badly infected pressure sore.

Fortunately, an improved understanding of SCI led to better patient management, enabling many people to survive their injuries and the initial period afterwards. In addition, the discovery of penicillin and sulfa drugs made common, but life-threatening complications manageable.

Because the spinal cord carries vital information between the brain, muscles and many organs, the fact that SCI is now a survivable injury is itself a miracle. However, this miracle leads to another pressing need – to find a way to reverse, or at least diminish the devastating physical effects of the injury.

The Search for a Cure

Recent years have been an exciting time for people interested in spinal cord injury repair and regeneration. Both in terms of treatment techniques and general knowledge about nervous system function, the progress that has occurred is very encouraging.

The search for a cure involves one of the most complex parts of the human body. The spinal cord is an integral part of the body's most specialized system, the *Central Nervous System.* The central nervous system consists primarily of the brain and spinal cord.

A major role of the spinal cord is to carry messages to and from all parts of the body and the brain. Some of these messages control sensation, such as knowing when your finger is touching a hot stove, while others regulate movement. The spinal cord also carries messages that regulate autonomic functions such as heart rate and breathing – over which we generally do not exert voluntary control.

The spinal cord carries these messages through a network of nerves, which link the cells of the spinal cord to target cells in all other systems of the body. An individual nerve cell is called a neuron, each with receptive branching fibers called dendrites. The axon, carrying an output signal, extends from the cell body, and is covered by protective fatty substance called a myelin sheath, which helps the impulse travel efficiently.

A nerve impulse from one neuron is picked up by the dendrite of the next nerve cell in the pathway at a specialized connection called a synapse. An electrochemical reaction causes the impulse to "jump" across the synapse and the signal stimulates the second nerve cell and the impulse then travels down its axon. The message is picked up and transmitted by a series of neurons until the connection is complete.

There are millions of nerve cells within the spinal cord itself. Some of these lower motor neurons receive motor commands from the brain and send their signals directly to the muscles. Other spinal cord neurons form relay pathways for information travelling up or down the length of the spinal cord. Still other spinal cord neurons remain intact and form intricate circuits below the level of injury. Because cells below the injury are no longer under voluntary control, they cannot be utilized as effectively and may cause unintentional movements, such as spasms.

Regeneration

Most of the cells in the human body have the ability to repair themselves after an injury. If you cut your finger, often you have a visible laceration for a few days or weeks, followed by the formation of a scar. In time, you may not be able to tell that the cut had occurred. This indicates that the skin cells regenerate, just like cells in blood vessels, organs, and many other tissues. Peripheral nerves (nerve fibers outside the brain and spinal cord), such as those located in your fingertips, also regenerate, although this process is different from that in the skin and other organs.

For years, scientists have focused on the big mystery: "Why doesn't the central nervous system regenerate?" This question is even more perplexing because we know that central nerves in the lower animal species can regenerate. There are no definite answers to this mystery yet, but scientists are exploring the questions in many ways.

Basic Cell Research

An important avenue of research is to look at normal cell function in the central nervous system of mammals. Scientists investigating this area of research are attempting to identify and describe cellular interactions in properly working system. In addition, they are working with SCI models in an attempt to identify and explain what occurs after an injury.Through cell research, scientists are trying to identify the following:

1. **What substances are present in the central nervous system which "switch off" nerve growth in mammals?**

   It has been shown that regeneration occurs in lower animals, as well as in mammalian fetuses in the very early stages of development. At some point in development, the cells appear to lose the ability to regenerate. This loss may be related to the maturation of the nerve cells or to changes in other nervous system cells past which axons must regenerate.

2. **What growth inhibiting factors present in the central nervous system of mammals prevent nerve cells from regenerating and reestablishing connections (synapses).**

   Scientists have identified some proteins in the myelin sheath surrounding spinal cord axons, which inhibit nerve cell growth. Additionally, other regeneration-inhibiting proteins have been identified on the surfaces of cells that form the nervous system equivalent of a scar. Some scientists believe that nerve cells can be encouraged to re-grow and reestablish functional synapses by removing or altering this cellular scar. Antibodies generated against some of these proteins can neutralize the inhibitors and allow growth to occur. The ability of central nerves to regenerate in lower animals is thought to be due to the lack of inhibitors in their central nervous system.

3. **Can growth-stimulating substances be introduced into the mammalian central nervous system to encourage nerve growth and synapse development?**

   Investigators are attempting to alter the environment around the injury site to encourage nerve cell growth and repair. The peripheral nerves can regenerate; this is due to the presence of cell proteins that stimulate, rather than inhibit, nerve growth. When these cells or the factors they produce, such as growth factors that nourish nerve cells, are introduced into the central nervous system, central nerve re-growth can occur. Finding ways to effectively introduce these cells or substances to achieve functional recovery is a major goal of cure research today.

Development of New Therapeutic Approaches

Ongoing research using animal models to test possible new therapies is progressing more rapidly than ever before. This type of research takes several forms that can best be explained as they apply to solving certain types of damage that result from spinal cord injury. There are three major classes of damage to neural tissues that have been identified, each requiring a different

therapeutic approach.

1. ***Death of nerve cells within the spinal cord.*** **Because nerve cells lose the ability to undergo cell division as they mature into the highly specialized forms that make up our nervous systems, the death of nerve cells due to injury presents a difficult problem. No functional connections can be established if the nerves no longer exist. Therefore, replacement of nerve cells may be required.**

2. ***Disruption of nerve pathways.*** **When the long axons carrying signals up and down the spinal cord are cut or damaged to the point where they break down after an injury, the parent nerve cells and axons often survive up to the point where the injury occurred. In this case, regeneration of damaged axons to re-establish connections of the nerve circuits is a real possibility.**

3. ***Demyelination, or the loss of the insulation around axons.*** **Animal studies and recent studies of human specimens have established that in some types of SCI, the nerve cells and axons may not be lost or interrupted, but that the loss of function may be due to a loss of myelin sheaths. Myelin sheaths provide insulation so that electrochemical signals are carried efficiently down the long axons. This type of damage may be the most amenable to treatment because rewiring of complex circuits may not be needed and remyelination of axons is known to be possible.**

   Although specific human injuries may involve any or all types of damage just described, therapies developed to combat any one of them might restore important functions. The cure for spinal cord injury may take the form of multiple strategies, each in turn restoring functions that make important improvement in the quality of life for a spinal cord injured individual.

The approach to cure research then is to concentrate on techniques that hold the promise of repairing specific types of spinal cord damage. With the explosion of efforts and progress in the fields of neuroscience and molecular biology (sometimes called genetic engineering), the scope of possible new therapies is wider than ever before.

Replacement of Nerve Cells

Mature nerve cells cannot divide to heal a wound as skin cells can. Replacement of nerve cells requires transplantation of new nerve cells into the site of the injury with the hope that they will mature and integrate themselves into the host nervous system. One approach is to transplant healthy central nervous system cells from the same animal species. Researches have been unanimous in their agreement that transplantation of adult nerve tissues does not work, while embryonic or fetal transplantation can be quite successful. The embryonic tissues do grow and develop below the injury. Research to date has not supported the hope that host axons would use these grafts as "bridges" across the injury site. An important consideration is that if fetal tissue transplants prove successful in animal models, transferring this approach to human being will involve important ethical considerations regarding donor tissues and other important questions about immune rejection of cells transplanted from one individual to another.

Another approach that may avoid some of those problems is the use of genetic engineering to manufacture "cell lines" that would work as nerve cells after grafting. This approach involves inserting segments of DNA (genes) into fetal nerve cells that allow the cells to divide indefinitely,

creating an ongoing supply of donor tissue. The use of purely neuronal cell lines diminishes the changes of immunological rejection of the grafts. Recently rodent cell lines have been developed that stop dividing after transplantation (so there is no risk of tumor formation), and that mature into very specialized nerve cells. Research has not yet shown that these cells can restore function after spinal cord injury.

Very recently, scientists have learned that some cells of the adult central nervous system can be stimulated to divide and develop into new nerve cells. This exciting finding has opened up new possibilities for cell line development without a need for fetal tissue donors.

Regeneration of Damaged Axons

Nerve cells in both the central and peripheral nervous systems are associated with helper cells called neuroglial cells. After injury, the central nervous system helper cells largely inhibit regeneration, while those of the peripheral nerves, the Schwann cells, stimulate regeneration. Scientists are attempting to isolate these cells from peripheral nerves and transplant them into the spinal cord to induce regeneration by providing an altered, supportive environment. In this strategy, a spinal cord injured individual could act as their own donor, since Schwann cells can be obtained from biopsies of peripheral nerves in adults.

Schwann cells, nerve cells and some other cells make proteins known to nourish nerve cells called "growth factors." By introducing these factors into injury sites alone or in combination with grafts, researchers hope to stimulate additional nerve regeneration and promote the health of nerve cells. This approach has been shown to stimulate central nervous system regeneration, including growth of axons from nerve cells within the spinal cord and those from the brain that send the long axons down the spinal cord. Significant restoration of function has not yet been achieved.

Another technique is to genetically alter cells so that they produce large amounts of growth factors and to introduce these into the injury site. While nerve fibers have been stimulated to grow by such grafts, this type of research is in its very early stages. Cells making many types of factors will have to be tested and functional recovery carefully demonstrated.

Remyelination of Axons

Schwann cells are also the cells in peripheral nerves that form myelin sheaths. They are not usually found in the brain or spinal cord where another neuroglial cell, the ogliodendrocyte is responsible for making myelin. Researches have shown that Schwann cells grafted into the brain can myelinate central axons. When the loss of myelin is an important part of injury, implanting Schwann cells could stimulate remyelination and thereby restore function.

Another approach involves a drug called 4-aminopyridine (4-AP) which may help demyelinated nerves conduct signals. Animal studies show that a very small percent of healthy, myelinated axons can be enough to carry on important functions in the spinal cord, even in the face of damage to surrounding nerve cells. Helping nerve fibers that have lost myelin to conduct impulses should improve functions after injuries that extensively damage myelin sheaths, but do not disrupt nerve connections. This research is also in its very early phases.

The problem of the central nervous system's response to injury is incredibly complex. No one theory or approach will overcome all of the effects of spinal cord injury and many scientists now believe that the "cure" will not be found in a single approach, but rather in a combination of techniques. Consequently, it is important for all possible research areas to be addressed so the overall knowledge about how the system works may eventually lead to a cure for SCI.

What about the "imminent breakthroughs" you hear about regularly in the press? It must be remembered that there is a vast difference between a scientific breakthrough and a clinical breakthrough. While scientific discoveries occur quite frequently, clinical treatments do not. Public announcements of scientific progress help to keep the attention and funding focused on finding solutions to the problems caused by SCI, but new scientific breakthroughs generally do not lead to immediate treatment applications.

Regeneration of Damaged Axons

Drug Treatments for New Injuries

It is important to realize these drugs are not a cure for chronic (long-term) spinal cord injuries. It is heartening to note, however, that treatments finally are available to lessen the severity of some acute injuries.

Research has shown that all damage in SCI does not occur instantaneously. Mechanical disruption of nerves and nerve fibers occurs at the time of injury. Within 30 minutes, hemorrhaging is observed in the damaged area of the spinal cord and this may expand over the next few hours. By several hours, inflammatory cells enter the area of the spinal cord injury and their secretions cause chemical changes that can further damage nervous tissue. Cellular content of nerve cells killed by the injury contribute to this harmful chemical environment. This process may go on for days or even weeks.

Hope lies, therefore, in treatments that could prevent these stages of progressive damage. Drugs that protect nerve cells following injury are now available to lessen the severity of some injuries. Other drugs and combinations of drugs are currently being tested in both animal and clinical trials.

Methylprednisolone

Few treatment approaches have raised as much hope as the announcement by the National Institute of Health that the steroid methylprednisolone reduces the degree of paralysis if administered shortly after a spinal cord injury.

In clinical trials, an extremely high dosage of methylprednisolone was used in a double-blind study (neither patients nor doctors knew who was getting the experimental drug). The improvement in some patients was so remarkable that the National Institute of Health felt it was important to "break the code" (determine who was getting the drug and who was not) so more patients could potentially be helped. Overall, the trial showed that while the methylprednisolone-treated group retained significantly more function than the placebo group, subjects in both groups experienced chronic loss of function due to their injuries.

Methylprednisolone is effective only if used in high doses within eight hours of acute injury. It is

hypothesized that this drug reduces damage caused by the inflammation of the injured spinal cord and the bursting open of the damaged cells. The contents of the damaged cells are believed to adversely affect adjacent cells. High does of methylprednisolone can lead to side effects, such as suppression of the immune system, but no serious problems have been reported when it is used over a short term, as in the study.

Because the success of the methylprednisolone trial had changed the standard of care in the United State, subsequent drug trials are now testing the effectiveness of other drugs in combination with methylprednisolone administration. Thus, to demonstrate significant effectiveness, new treatments will have to surpass the functional sparing effects seen with methylprednisolone alone. Simultaneously, researchers are cooperating to conduct a large, multi-center animal study to test the effect of other drugs with or without methylprednisolone.

Tirilizade

Similar positive results to those of methylprednisolone have been achieved in animal studies using another steroid, tirilizde mesylate (Freedox®). This drug, which acts like methylprednisolone, also appears to be effective only if administered within a few hours after injury. From initial studies, it appears that this drug may cause fewer side effects than methylprednisolone. Clinical trials are ongoing. A large clinical trial with humans is currently underway, comparing 48-hour treatment of methylprednisolone, with or without added tirilizade. Analysis of the data is ongoing at this point.

GM-1 Ganglioside

In a small study, the experimental drug Sygen®, or GM-1 Ganglioside, was given within 72 hours of injury and then continued for up to 32 days. Neurological assessments were conducted up to one year after the treatment.The following summary was prepared by Fidia Pharmaceutical Corporation based on a presentation by Fred H. Geisler, M.D., Ph.D., of the Chicago Institute of Neurosurgery and Neuroresearch on October 8, 1998.

"The Sygen® Acute Spinal Cord Injury Study presented at the Congress of Neurological Surgeons in Seattle on October 8, 1998 is the largest prospective study ever completed on treatment of spinal cord injuries. Over a five-year period, 28 North American neuro-trauma center enrolled 797 patients with injuries ranging from the most severe to relatively mild. Patients were treated for eight weeks with either Sygen® or placebo after methylprednisolone therapy. Analyses completed to date show that while the difference in recovery rates six months after injury was not statistically significant, there was a clear pattern of enhanced recovery among Sygen®-treated patients. Because of the magnitude and complexity of the study, analysis of the full database of information – containing approximately eight million entries – is still underway. Additional results will be released after completion of the remaining analyses. On the basis of the evidence available to date, the company is currently pursuing the registration of Sygen® in the United States and Canada.

There are two theories about how GM-1 Ganglioside may act on spinal cord tissue. The first is that it performs some type of damage control by reducing the toxicity of amino acids released after spinal cord tissue is injured. The "excitatory" amino acids cause cells to die and increase the damage caused by the initial injury. The second theory suggests there may be a neurotrophic effect, somehow encouraging the growth of injured neurons. Neither of these theories has been scientifically proven yet. The FDA has not yet approved Sygen® for clinical use.

Surgery

Clinical studies are being conducted by surgeons to determine the optimum time for surgery to relieve pressure on the spinal cord after spinal cord injury. Additionally, the use of delayed decompressive surgery is being investigated in cases of chronic SCI.

Preventing New Injuries During Spinal Surgery

Intraoperative monitoring techniques have been developed to protect healthy nerve roots during spinal stabilization procedures. Scientists tested, first on animals then on humans, a technique that assists surgeons in the placement of metallic hardware for stabilizations of the spine. The technique, which utilizes nerve stimulation and muscle responses, has been shown to effectively predict and allow the prevention of nerve damage during surgery in the lumbosacral spinal column.

Treatments for Chronic Spinal Cord Injury and its Complications

Functional Electrical Stimulation

Functional Electrical Stimulation (FES) uses implanted electrodes to stimulate paralyzed nerves so that arms and legs can be used for improved function. Primary applications for FES include the following: FES for exercise, FES for upper extremity (hand/arm) function, and FES for lower extremity (leg function) and FES for bowel and bladder control. FES is discussed in detail in the fact sheet entitled "Functional Electrical Stimulation: Clinical Applications."

Omentum Transition

One controversial treatment for SCI is Omentum Transposition. The omentum is a band of tissue in the abdomen of mammals, which provides circulation to the intestines. A surgical procedure is used to partially detach the omentum, tunnel it under the skin and suture it in place at the injury site. The omentum tissue, which is rich in blood vessels, may supply the damaged nerve cells with vital oxygen. It is believed that the omentum tissue may also secrete chemicals that stimulate nerve growth, as well as have the ability to soak up fluids to reduce pressure which can damage nerve cells.

Initial animal trials seem to show some functional improvement if the operation is completed within three hours of injury. Little or no improvement is shown when the procedure is done six to eight hours post injury. This research, however, has never been scientifically documented. The on-going clinical trial for people who have had a SCI for months or years has been canceled, since the results of earlier research have not been sufficiently documented.

Biomedical Engineering

Scientists in the field of biomedical engineering developed mechanical devices that use today's computer technology to assist individuals in activities of daily life. Examples of the types of devices under research and development are environmental control devices, electronic handgrip devices and walking devices.

Spasticity and Pain

The complications of spasticity and pain are common in spinal cord injury. Spasticity that is severe enough to cause problems with mobility and self-care, that contributes to skin breakdown, and that causes pain is reported in a number of cases of SCI.

Studies in the treatment of spasticity are investigating pharmacological agents, intrathecal baclofen, and spinal cord stimulation. In addition to drugs that have been available for some time (baclofen, valium and dantrium), the use of trizanidine is being explored.

The problem of pain occurs in approximately 50% of all cases of SCI. Five to thirty percent characterize the pain as disabling. Pharmacologic agents, as well as surgical interventions such as the DREZ (dorsal root entry zone) procedure, cordotomy and cordectomy, are under investigation for the treatment of severe causes of pain from SCI.

Male Fertility

In most SCI men, the ability to have an ejaculation and to father a child naturally is diminished. In fact, ten years ago, doctors were telling newly injured SCI men that they would not be able to father their own children. With advances made in procedures to assist men in obtaining an ejaculation as well as advances in assistive reproduction technology, SCI men now have the potential to become biological fathers. Vibratory stimulation and electroejaculation are procedures that have been investigated and are currently available to assist men in obtaining ejaculations.

Obtaining the ejaculation is only part of the fertility problem in SCI men, however, the semen from SCI men most often contains a lower than normal percent of motile sperm. Questions that researchers hope to be able to answer with investigations on the quality of sperm of SCI men are: what happens to semen quality following SCI and, how successful is artificial insemination and other reproductive technology using semen from SCI men.

Technology and research are making it possible for spinal cord injured men to consider options regarding their fertility and is providing a more encouraging answer to the question "Will I be able to have children?"

Alternative Therapies

Various controversial treatments for SCI have come and gone over the years, but none have proved to be effective in reversing the damage to the spinal cord that occurs in spinal cord injury. Often alternative therapies are very difficult to evaluate because of the unscientific nature in which the treatments are introduced to the human population. Many alternative therapies have no documented scientific evidence to substantiate their effectiveness. Currently, examples of treatments that fall into this category are the use of Sygen® (GM-1) in chronic injuries and omentum transposition.

Over the last several years there has been progress in the treatment of acute SCI to limit damage and preserve function. Treatment of chronic SCI presents a greater challenge, as damage that has already occurred must be corrected and then reversed.

It is entirely possible that, given appropriate financial support, many of the complex problems of SCI one-day will be solved. Until that day arrives, it is important to urge the federal government to provide broad-based support for basic science research so the fundamental questions about

how and why the CNS acts the way it does can be answered. A cure or new treatments are possible only if scientists receive the support necessary to continue their work in this important area.

For further information on Freedox® clinical trials, contact: Upjohn Company, 929 Lawrence Court, N. Bellmore, NY 11710, 516-486-5276.

For further information on Sygen® clinical trials, contact: Fidia Pharmaceutical Corp., 1401 I Street, NW, #900, Washington, DC 20005, (202) 371-9898 x334.

For further information about FES applications, contact: F.E.S. Information Center, 25100 Euclid Avenue, Suite 105, Cleveland, Oh 44117, (800) 666-2353.

For further information about The Miami Project, contact: The Miami Project, 1600 Northwest 10th Avenue, R-48, Miami, FL 33136, (800) STAND-UP.

Suggested Readings

Books:

Maddox, Sam, (1992): The Quest for Cure: Restoration of Function after Spinal Cord Injury, Paralyzed Veterans of America, 801 18th Street, NW, Washington, DC 20006.

U.S. Department of Health and Human Services, National Institutes of Health, The NINDS Research Program, (1989): Spinal Cord Injury, NIH-NINDS, Building 31A, Room 8A16, 9000 Rockville Pike, Bethesda, MD 20892.

Newsletters and Magazines:

International Spinal Research Trust Newsletter, International Spinal Research Trust, Nicholas House – River Front, Effield, Middlesex, England.

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The Road Toward a Cure for Spinal Cord Injury

This article is from the Pushin' On Newsletter, Vol 20[1], February, 2002. Published by: The Medical RRTC on Secondary Conditions of SCI, 619 19th Street South - SRC 529, Birmingham, AL 35249-7330.

by Phil Klebine

When *Pushin' On* was first published in 1982, there was not a lot of money funding research for a **cure** for spinal cord injury (SCI). Sure, individuals with SCI have always had hope for a **cure**, but most scientists use to believe that a **cure** for paralysis was highly unlikely. The notion of **nerve regeneration** in the spinal cord seemed impossible, so money was more often spent on areas of research that did not focus on a **cure**.

A **cure** became increasingly probable as progress toward **nerve regeneration** improved. Today, no one knows if it will take 5, 10, or even 20 years or more, but most scientists now agree that it is only a matter of time before there is some form of **cure**. In fact, this promise of a **cure** has opened the door for a new attitude. There are now millions of dollars spent each year on research with the very real possibility that a **cure** is within reach.

This possibilty of a **cure** has individuals with SCI asking some very interesting questions. Why is it so hard for doctors to find a **cure**? When there is a **cure**, what will it be? Will I be able to get back all my lost motor and sensory functions? What can I do to help?

What Are the Difficulties in Finding A Cure?

First, every spinal cord injury is different. Some injuries are caused by car accidents and others by falls. Injuries occur at different levels, and some people have complete injuries while others have incomplete injuries. All of these factors mean that some injuries result in a more severe loss of sensory and motor function than others.

Second, further damage to the spinal cord can occur beyond the time of the initial injury. For example, swelling occurs around the injured area of the spinal cord within hours after injury. The swelling causes additional damage to **nerve** axons and blood vessels. In addition, the regrowth of **nerve** cells is later blocked by substances that the body naturally produces to inhibit **nerve** growth. These biological complications are some of the main factors that contribute to the difficulties of finding a **cure**.

When There Is A Cure?

When you think about a **cure** for paralysis, you might imagine many possibilities. You might think that you will need surgery to repair the damaged nerves in your spinal cord. You may be hoping that you can simply take a pill each day and gradually regain function.

Current scientific evidence suggests that there will not be one simple **cure**. It is not likely that one surgical treatment or one special medication will solve all of the complexities that are involved in restoring function. Instead, a **cure** will likely involve a combination of different treatments working together. For example, a **cure** might eventually involve a surgical procedure to enhance **nerve regeneration**, and various drug treatments may be necessary to promote the reestablishment of **nerve** connections.

How Will A Cure Work?

A *Research Review*[1] of the latest research for a **cure** of spinal cord injury is now available. The newsletter explains that persons who are newly injured and persons who have been injured for many years will likely benefit from different strategies for a **cure**. However, the newsletter notes four strategies toward a **cure** that are currently being funded. An eventual **cure** for paralysis will likely involve the use of one or more of four areas of research.

Neuroprotective Agents

When a person is first injured, there is obvious damage to nerves and cells at the site of the injury. This damage is often severe enough to result in spinal shock (a temporary form of **nerve** paralysis) or complete or partial paralysis of the person's motor and/or sensory function. In addition, further damage to the spinal cord's **nerve** cells and its protective covering (myelin) continues for days or even weeks after the initial injury.

Researchers hope to solve this problem by using specific types of medications that prevent or counteract the death of **nerve** cells after injury. Some examples of these medications include Methylprednisolone, GM-1 Ganglioside (Sygen), Interleukin-10, and Gluamate (AMPA) Receptor Blockers.

Regeneration

Regeneration, or getting nerves to grow, is a difficult process. Unlike many peripheral nerves that flow from the spinal cord throughout the body, central nerves within the spinal cord do not usually regenerate when damaged. The reason is that spinal cord tissue contains certain chemicals that actually stop **nerve regeneration**.

Based on laboratory success, researchers believe that they can promote **nerve** regrowth and block the chemicals that prevent spinal **nerve** growth. However, their attempts to reestablish the correct "connections" on both sides of the injury have been unsuccessful thus far in humans. Researchers are studying the effectiveness of many different possibilities to solve the many problems of **regeneration**.

Transplantation

When damage occurs to nerves outside the central nervous system (the brain and spinal cord), those peripheral nerves sometime regenerate. Researchers are trying to replace damaged central **nerve** cells that do not regenerate with peripheral **nerve** cells that do regenerate. Their belief is that the transplanted **nerve** cells will continue to regenerate and become a part of the central nervous system.

One transplantation option has recently generated a lot of debate. Fetal Central Nervous System Tissue is believed to help with **nerve regeneration**. The tissue contains stem cells, progenitor cells and other substances that support **nerve** growth. These stem cells can develop into several cells depending on the types of signals they receive. Researchers hope that transplanting stem cells into the spinal cord will result in **nerve** regrowth and connection.

Rehabilitation

An essential element of any hope for a **cure** is rehabilitation. No one is going to simply get up and walk. It will take time. You will have to work extremely hard to regain strength, stamina, and balance. Your brain may need time to relearn how to communicate with your body to improve function. All of this work will require a number of different therapies to be most effective.

What Kind of Return Will I Have?

As an individual with SCI, you may be hoping that research for a **cure** will result in a full recovery from your injury. You may expect to return to your old, "normal" self. You might image yourself doing daily activities with the same ease as

before your injury. This is the goal of research for a **cure**, but it will take a long time to reach that goal.

Although this image of a full recovery may become a reality in the future, it is much more likely that you will first benefit from research that improves your current function or gives you partial recovery. For example, researchers are working to improve function in parts of the body such as the bladder and bowel. There is also a lot of work currently in the area of Functional Electrical Stimulation (FES). FES is the process of sending electrical stimulation to muscles to improve function. These are only two examples of work being done to improve current quality of life.

What Can I Do?

Most all individuals with spinal cord injury want to benefit from a **cure** for paralysis. It is only logical that you want to get as much benefit as you can from treatments to improve quality of life. You can help improve your chances for benefitting from scientific advances by doing everything possible to take care of your body and stay healthy.

As an individual with SCI, you are at risk for medical complications such as pressure sores, urinary tract infection and respiratory infections or illness. If you do not take care of your health, you put yourself at an even greater risk. Many medical problems can severely limit your ability to exercise and lead an active life. Some complications are also life-threatening.

The single most important thing that you can do to benefit from research for a **cure** is to prevent medical problems. Take care of your body, and stay active. It is recommended that you get regular, annual checkups from your doctor to help prevent long-term health problems.

Losses in bone density and muscle mass are two other obstacles that need be considered when thinking about walking. You have likely lost muscle and bone mass due to a lack of use. This loss is common after injury. Unfortunately, the natural physical changes that come with aging and menopause can result in added bone and muscle loss.

You may not be able to completely stop the loss of bone and muscle, but you can help minimize your loss. First, talk to your doctor and establish a healthy diet and exercise program. These programs can help you stay healthy and active. Plus, proper diet and exercise programs can improve your chances of getting the most from possible treatments to improve function.

Participating in Research

You may want to participate in some current or future

research in spinal cord injury. Researchers are almost always recruiting individuals with SCI to participate in clinical studies to determine the effectiveness of treatments. Researchers will also one day recruit persons to participant in research for a possible **cure** for paralysis. If you want to participate in any kind of research, you should understand the realities of research. It is logical to think that researchers will almost certainly want those individuals with SCI who will offer the best hope for success. Therefore, it is likely that researchers will first accept participants who are healthy and active. If you are not active or if you have medical problems, you may not get the opportunity to participate in research.
Individuals with paraplegia will likely be the first to participate in research to improve motor or sensory function. The reason is that a person with low level of injury is at less risk for losing function if the research fails. For example, an individual with a T5 injury does not lose much function if a research project fails and leaves the person with a T3 level of injury. On the other hand, an individual with C5 level of injury can lose a lot of functional abilities if a research project fails and leaves the person with a C3 level of injury. Researchers are not likely going to take risks with function until the benefits of treatment are proven to far outweigh the risks.

Conclusion

Individuals with SCI will always hope for a **cure** for paralysis. Today, medical advances have led to the likelihood that some type of **cure** is within reach. It is now up to you to prepare yourself for the **cure**. What you do today may have a direct impact on how well you will benefit from research to improve some, or all, of your body's functions. You want to do everything you can to help improve your chances of benefitting from research for a **cure**. It is up to you to be ready when there is finally a **cure** for spinal cord injury.

[1]Craig, M; Lindsey, LL. Research Review. Spring 2002. To recieve a copy of this newsletter, go to www.spinalcord.uab.edu/show.asp?durki=19803

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Human Cloning: Science Fiction or Reality?

Gr

On 27th December, 2002, Dr. Brigitte Boissilier, scientific director of Clonaid, claimed the birth of the first cloned announcement was greeted with revulsion from the general public and skepticism among the scientific communit the world still awaits scientific verification of this procedure, the claim intensified the ongoing public debate regard technology and its potential uses. Cloning has been hypothesized to have the potential to revolutionize at least tw human life.

Therapeutic cloning aims to produce embryonic stem cells which, because of their multipotentiality, have been pr source of cells for the replacement of damaged or defective tissue in adults. In this form of cloning, cells are neve develop into a complete organism. Reproductive cloning, on the other hand, aims to produce offspring with simila identity to previously existing organisms. This practice raises many ethical and moral questions.

Embryonic Stem Cells: A Cure for many diseases?

Several adult tissues, once damaged, are **not** able to repair themselves. The neural system is the most obvious e this. When someone sustains **spinal chord injury**, the body is unable to repair the neurons in the **spinal chord** a person remains paralyzed for life. This is in direct contrast to other tissues such as the blood and skin, where mill are lost and replaced each day. Stem cells, which have the ability to become these mature or differentiated cells, responsible for maintaining tissues at constant levels. Unfortunately, stem cells are generally difficult to find in adu they are isolated, they are often hard to grow into cell lines. It is unlikely that adults will be a sufficient source of st therapeutic purposes. Embryonic stem cell lines have the potential to divide indefinitely and are pluripotent (they l potential to differentiate into various types of cell). An important consideration in therapeutic cloning is the possibi patient's immune system will reject the transplanted cells. Each patient is an ideal donor for himself or herself bec abolishes the need to find a donor with compatible tissues. Cloning the individual to create unlimited stem cells w ideal way to circumvent this situation.

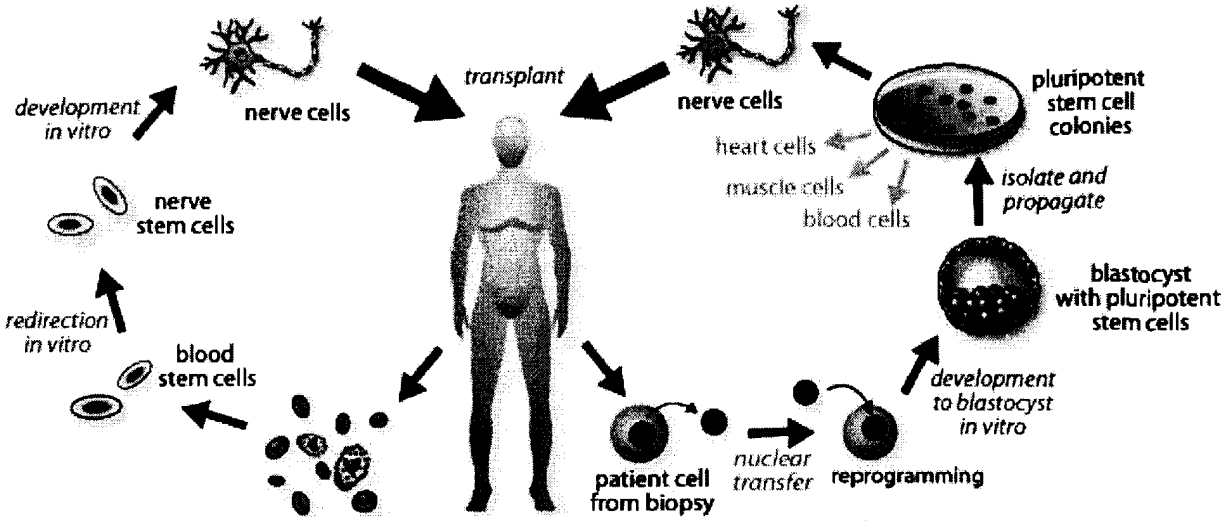

Figure 1. Somatic cell nuclear transfer. Here, a skin cell is removed from a patient. The nucleus of this placed inside an enucleated oocyte and stimulated to divide. The resulting blastocyst can either be us make embryonic stem cells, which are genetically identical to the donor, or they can be brought to ter create a genetically identical human being.

stem cells continues, the source of these cells will become an issue. Embryonic stem cells are taken from the ear shortly after fertilization. At present, embryos that are frozen for couples undergoing in vitro fertilization are used f embryonic stem cells. Generally, due to the high failure rate of the procedure, multiple eggs are fertilized and stor are then transplanted into the mother one at a time until she becomes pregnant. The remaining embryos remain i and are generally forgotten. They present a potential limited source of stem cells as long as the issue of tissue re addressed.

More recently a new technique has been developed called somatic cell nuclear transfer (SCNT). SCNT involves t of an egg from a hormonally treated female. The donor egg is enucleated and the nucleus of a somatic cell is trar its cytoplasm (nuclear transfer). The egg is then stimulated to start dividing. After sequential cell divisions, the bla formed contains cells that will give rise to all tissues in the embryo. The blastocyst can be used to generate embr cells, which are genetically identical to the somatic cell donor, thereby eliminating the possibility of rejection when transplanted.

Reproductive cloning

Alternatively, the blastocyst can be implanted back into a female and brought to term resulting in a cloned organis procedure was allegedly used in the production of the first cloned human mentioned above.

SCNT was pioneered by Dr. Ian Wilmut at the Roslin Institute in Scotland. He used this technology to produce the cloned sheep, Dolly, in 1996. Unfortunately, she developed arthritis early in life and showed premature signs of a was euthanized in February 2003 after doctors detected a progressive lung disease. She had only reached half th a typical sheep and, while it has **not** been proven that her cloned status played a part in her early death, scientist sensitive to the fact that the full implications of this technology are **not** yet **known**. Since 1997, this technology ha to clone pigs, mice, goats and cats. In November 2001, the production of the first human embryo by this method v in the Journal of Reproductive Medicine.

Human reproductive cloning has considered unethical by the scie community due to safety consid According to animal studies, prc healthy reproductive clone will c potential morbidity and mortality carrying cloned fetuses, newbor donors. In animal studies, only

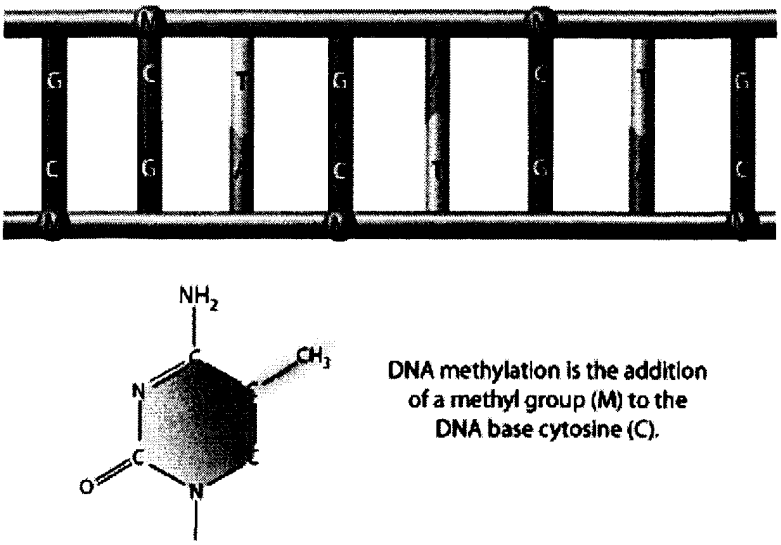

Figure 2. DNA Methylation

cloned zygotes survive to the bi
Therefore, a large number of eg
needed to get a successful birth
obtain enough eggs for one suc
many women will need to donat
Studies on in vitro fertilization sh
is a risk of ovarian hyperstimula
associated with egg donation, w
sometimes cause maternal deat

There are also complications in
carrying a cloned animal to term
of abortion and neonatal loss ha
observed. There have also beer
gestational abortions. This is in
the early spontaneous abortion
naturally in humans during the fi
Fetal abnormalities are also abu
abnormal placenta, pregnancy t
hydroallantois (excessive fluid a
all frequently occur and result in fetal abnormality. Consequently, newborns often die. High rates of late gestation
including stillborns and children with severe health problems would have a negative psychological effect on moth
Furthermore, in the event that an infant is born, there is a high probability that it will **not** be healthy. A wide variet
and organs fail to develop properly. Many cloned animals have been born with abnormalities such as respiratory
immune deficiency, inadequate renal function, cardiovascular problems, large birth size, post natal weight gain, a
joint defects. In addition to these problems, human clones would have a risk of aberrant brain development. Brain
development problems in animals could easily have gone undetected in the past, and human brain development
complex than that of animals. This list of defects cannot be diagnosed or prevented using current technology of p
screening or ultrasonography. The possible benefits of human reproductive cloning do **not** seem to justify the risk
parties involved.

The current problems with mammalian reproductive cloning are likely related to faulty epigenetic reprogramming.
Reprogramming is the process by which DNA and its associated proteins (in a nucleus transplanted from a soma
reset to coordinate early developmental processes. When SCNT is performed, the adult nucleus needs to respon
cytoplasm as though it were a nucleus of a zygote. Theoretically, this will shut off the genes that are active in adu
would normally be inactive in a zygote. Reprogramming needs to occur in a relatively short time, a few days in m
In sexual reproduction, reprogramming is **not** necessary as genes are derived from germ cells. The egg and sper
preprogrammed during the egg and sperm development and continues throughout early development. Programm
thought to occur by imprinting.

Imprinted genes have a "mark" imposed on or near them. The most well studied mode of "marking" is methylation. Imprinting patterns are distinct in maternal and paternal genes. This causes differential behavior of genes depending on whether it has maternal or paternal imprinting. Thus, the behavior of the allele is different depending on whether the chromosome came from the father or the mother. Mouse studies in which an embryo was created from two maternal derived gametes resulted in fetal abnormality and death. In humans, mutations that disturb the inactivation of genes can result in tumors in both children and adults. Some well **known** genetic disorders in children are caused by mutations in regions of DNA methylation, the imprint control regions. These diseases, including Angelman Syndrome and

Beckwith-Weidemann Syndrome, result in a combination of mental retardation and congenital abnormalities.

Nature versus nurture

There is a common perception that cloning an individual will create someone identical in every physical way. However, the clone will be distinct from the nuclear donor in many respects. Observations from human twins (natural clones) and cat clones have shown that identical genetic material is **not** the only determinant of character and appearance. Dissimilarities in human clones will be caused by different mutations, stochastic development, various imprinting effects, differing environmental and nutritional inputs while in the uterus and different societal inputs. Cloning will **not** necessarily reproduce the character, appearance and physiology of the nuclear donor. Studies with the cat Rainbow and her cloned copy (named Cc for carbon copy) are a good demonstration of this.

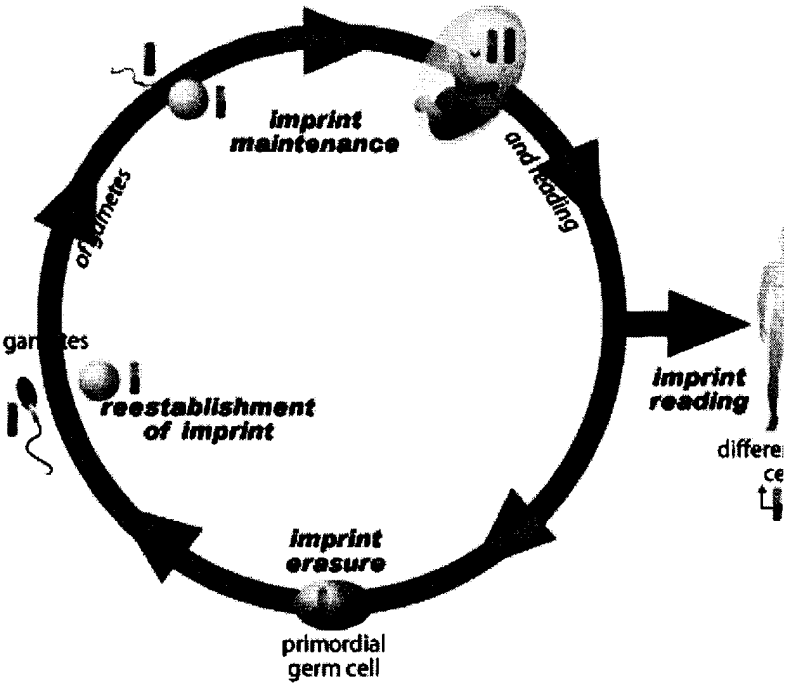

Figure 3. Imprinting cycle - Imprinting occurs in primordial ge during fetal development.

The cloning of Rainbow has demonstrated that the phenotype of the individual is largely determined by environm This project was funded by Genetic Savings & Clone, a company interested in cloning pets, and performed by re Texas A&M University. Their paper, published in Nature in 2002, presented the details of their project, including D that showed Cc was a clone. Interestingly, Rainbow and Cc have difference coat color and patterning, personaliti type. Rainbow is reserved while Cc is curious and playful; Rainbow is chunky while Cc is sleek.

There are practical purposes for animal reproductive cloning. Livestock, such as cattle, are a prime target for repr cloning. It allows breeders to avoid the randomness of natural sexual reproduction. Consistent replication of exist trait combinations such as efficient growth and high milk production is possible.

Current attempts to clone a human

Allegedly, there has been some progress in producing human embryos for therapeutic purposes. There has **not**, been any good scientific evidence presented to confirm these experiments. Nuclear transfer was reported with hu cells in the Journal of Reproductive Medicine in 2001. The embryo needs to reach the 64 cell stage before it can derive embryonic stem cells. It is still considered scientifically significant that one cell multiplied to the 6 cell stage represent progress in human reproductive cloning. The validity of the experiments has been questioned due to th resigning from the editorial board of the journal because they believed there was insufficient experimental validati authors failed to provide evidence that DNA from dividing cells came from the donor cell or that the cells were fun

Several people claim that they have gone farther than the early embryo stage and have successfully cloned a hu are currently attempting to do so. As mentioned earlier, Dr. Brigitte Bosselier from Clonaid, claims to have cloned babies. Clonaid is a company funded by the Raëlian Movement that is devoted to creating human clones. They h provide DNA samples or any other reliable evidence to support these claims. Clonaid says it has a list of 2,000 pe to pay $200,000 to have themselves or a loved one cloned. Dr. Severino Antinori and his collaborator, Dr. Panos Zavos announced in Nov. 2001 that 200 couples in an un-named European country would attempt to give birth to human clone. The births were expected to occur in the second-half of 2002, presumably following the traditional r gestation period. No results have been announced.

Legislation

Despite a lack of evidence to show that a human has been cloned, announcements by the Raelians and the cloni the sheep have resulted in the development of several laws. In the United States, Congress has passed a bill tha all human cloning (this bill has yet to be passed by the senate). Most countries, including Canada, do **not** have sp laws. Canada is in the midst of debating Bill C-13, the Assisted Human Reproduction Act. The Council of Europe protocol banning human reproductive cloning research defined as "any intervention seeking to create a human be genetically identical to another human being, whether living or dead." The interpretation of "human being" accordi domestic laws will be used to decide if this includes stem cells. Moreover, UK, Ireland and Germany did **not** sign but they previously had laws or they have implemented their own laws. Ireland and Germany have forbidden rese embryos for many years. The UK has banned reproductive cloning but SCNT for experimental treatment is **not** pr Human cloning claims have spurred governments to create regulations governing human cloning before rather th laws are required.

Conclusion

As of yet, human reproductive cloning still seems to be science fiction. Current medical and scientific evidence su is dangerous to both mother and child. Successful reproduction of a healthy human child is unlikely and **not** worth involved. The current claims made by religious factions are likely false. They have, however, served the purpose governing bodies and society to contemplate issues related to both therapeutic and reproductive cloning.

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FAQs

Klassen, H., Ziaeian, B., Kirov, I.I., Young, M.J., **Schwartz, P.H.** "Isolation of Retinal Progenitor Cells from Postmortem Human Tissue and Comparison with Autologous Brain Progenitors" J. Neurosci. Res., in press (2004), with cover.

The goal of the present study was threefold: to determine whether viable human retinal progenitor cells (hRPCs) could be obtained from cadaveric retinal tissue, to evaluate marker **expression** by these cells, and to compare hRPCs to human brain progenitor cells (hBPCs). Retinas were dissected from post-mortem premature infants, enzymatically dissociated, and grown in the presence of epidermal growth factor and basic fibroblast growth factor. The cells grew as suspended spheres or adherent monolayers, depending on culture conditions. Expanded populations were banked or harvested for analysis by RT-PCR, immunocytochemistry, and flow cytometry. hBPCs derived from forebrain specimens from the same donors were grown and used for RT-PCR. Post-mortem human retinal specimens yielded viable cultures that grew to confluence repeatedly, although not beyond 3 months. Cultured hRPCs expressed a range of markers consistent with CNS progenitor cells, including **nestin**, vimentin, Sox2, Ki-67, GD2 ganglioside, and CD15 (Lewis X), as well as the tetraspanins CD9 and CD81, CD95 (Fas), and MHC class I antigens. No MHC class II **expression** was detected. hRPCs, but not hBPCs, expressed Dach1, Pax6, Six3, Six6, and recoverin. Minority subpopulations of hRPCs and hBPCs expressed doublecortin, β-III tubulin, and glial fibrillary acidic protein, which is consistent with increased lineage restriction in subsets of cultured cells. Viable progenitor cells can be cultured from the post-mortem retina of premature infants and exhibit a gene **expression** profile consistent with immature neuroepithelial cells. hRPCs can be distinguished from hBPC cultures by the **expression** of retinal specification genes and recoverin.

Beilina, S., Tassone, F., **Schwartz, P.H.**, Sahota, P., and Hagerman, P.J. "**Redistribution of transcription start sites within the FMR1 promoter region with expansion of the downstream CGG-repeat element**" Hum. Mol. Genet. 13:543-549 (2004).

Fragile X syndrome, the most common form of mental impairment, is caused by expansion of a (CGG)n trinucleotide repeat element located in the 5' untranslated region of the fragile X mental retardation 1 (FMR1) gene. Repeat expansion is known to influence both transcription and translation; however, the mechanisms by which the CGG element exerts its effects are not known.

In the current work, we have utilized 5'-RLM-RACE to examine the influence of CGG repeat number on the utilization of transcription start sites in normal (n<55) and premutation (54<n<200) cell lines of both non-**neural** (lymphoblastoid) and **neural** (primary astrocyte) origin.

Our results demonstrate that, in both **neural** and non-**neural** cells, transcription of the FMR1 gene is initiated from several transcription start sites within a approximately 50 nt region that lies approximately 130 nt upstream of the CGG repeat element. For normal alleles, most transcripts initiate from the downstream-most start site, close to the single position identified previously. Surprisingly, as the size of the CGG repeat expands into the premutation range, initiation shifts to the upstream sites, suggesting that the CGG element may act as a downstream enhancer/modulator

of transcription. The shift in start site selection for both **neural** and non-**neural** cells indicates that the effect is general. Furthermore, the correspondence between start site utilization and the degree of elevation of FMR1 mRNA suggests that a substantial fraction of the increased message in the premutation range may derive from the upstream start sites.

Fuja, T.J., **Schwartz, P.H.**, Darcy, D. and Bryant, P.J. "**Asymmetric Localization of LGN but not AGS3, Two Homologs of Drosophila Pins, in Dividing Human Neural Progenitor Cells.**" J. Neurosci. Res. 75:782-793 (2004), with cover.

Human **neural** progenitor cells (hNPCs) can be recovered from postmortem human brains and used to study the molecular basis of neurogenesis. Human NPCs are being used to investigate the molecular basis of cell fate determination during stem cell divisions, based on comparison with the Drosophila model system. Drosophila neuroblasts and sensory organ precursors undergo well-defined asymmetric cell divisions (ACD), under the control of a genetically defined set of apical and basal determinants that are localized tightly and dynamically during division.

We show by indirect immunofluorescence, confocal microscopy, and time-lapse video-microscopy that LGN and AGS3, two human homologs of the Drosophila ACD determinant Pins, have distinct patterns of localization in hNPCs. When cells are grown under conditions favoring proliferation, LGN is distributed asymmetrically in a cell cycle-dependent manner; it localizes to one side of the dividing cell and segregates into one of the daughter cells. When the cells are grown under conditions favoring differentiation, LGN accumulates in double foci similar to those containing the mitotic apparatus protein NuMA, and in a pattern shown previously for LGN and NuMA in differentiated cells. AGS3, a slightly more distant Pins homolog than LGN, does not show asymmetric localization in these cells. The progenitor cell marker **nestin** also localizes asymmetrically in colcemid-treated hNPCs and colocalizes with LGN. The results suggest that hNPCs undergo ACD and that similar molecular pathways may underlie these divisions in Drosophila and human cells.

Schwartz, P.H., Bryant, P.J., Fuja, T.J., Su, H., O'Dowd, D.K., and Klassen, H.K. "**Isolation and Characterization of Neural Progenitor Cells from Post-Mortem Human Cortex.**" J. Neurosci. Res. 74:838-851 (2003), with cover.

Post-mortem human brain tissue represents a vast potential source of **neural** progenitor cells for use in basic research as well as therapeutic applications. Here we describe five human **neural** progenitor cell cultures derived from cortical tissue harvested from premature infants. Time-lapse videomicrography of the passaged cultures revealed them to be highly dynamic, with high motility and extensive, evanescent intercellular contacts. Karyotyping revealed normal chromosomal complements. Prior to differentiation, most of the cells were **nestin**, Sox2, vimentin, and/or GFAP positive, and a subpopulation was doublecortin positive. Multilineage potential of these cells was demonstrated after differentiation, with some subpopulations of cells expressing the neuronal markers beta-tubulin, MAP2ab, NeuN, FMRP, and Tau and others expressing the oligodendroglial marker O1. Still other cells expressed the classic glial marker glial fibrillary acidic protein (GFAP). RT-PCR confirmed **nestin**, SOX2, GFAP, and doublecortin **expression** and also showed epidermal growth factor receptor and nucleostemin **expression** during the expansion phase. Flow cytometry showed high levels of the **neural** stem cell markers CD133, CD44, CD81, CD184, CD90, and CD29. CD133 markedly decreased in high-passage, lineage-restricted cultures. Electrophysiological analysis after differentiation demonstrated that the majority of cells with neuronal morphology expressed voltage-gated sodium and potassium currents. These data suggest that post-mortem human brain tissue is an important source of **neural** progenitor cells that will be useful for analysis of **neural** differentiation and for transplantation studies.

Palmer, T.D., **Schwartz, P.H.**, Taupain, P., Kaspar, B., Stein, S.A., and Gage, F.H. "**Cell Culture: Progenitor cells from human brain after death**" Nature 411:42-43 (2001).

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Curis gains patent covering treatment of spinal cord injury, ALS

04/22/2004 10:37 AM

Cambridge-based Curis Inc. says it has been issued a U.S. patent for the **treatment** of motor **neuron injury** and neuropathy.

The claims of this patent recite methods of treating motor **neuron** disorders by activation of the bone morphogenetic protein (BMP) pathway through the administration of a BMP-7 related protein. Among the nerve disorders claimed are spinal cord **injury**, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) and peripheral neuropathies caused by **injury** or disease.

In November 2002, Curis exclusively licensed this patent and other related patents and patent applications associated with the BMP pathway to Ortho Biotech, a subsidiary of Johnson & Johnson. Ortho Biotech has sole responsibility for the development of BMP product candidates for the clinical indications mentioned above.

Curis is a therapeutic drug development company. Its focus is on regulatory pathways that control repair and regeneration.

Its stock (Nasdaq: CRIS) opened today at $4.68 per share, up 11 cents from yesterday's close.

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Spinal Cord Regeneration

Dateline: 01/27/00

Scientists at King's College London in England recently announced that they have successfully regenerated sensory **nerve** fibers back into the spinal cord of rats. This was an astonishing breakthrough as prior to this research, damaged sensory nerves were not able to grow back into the spinal cord.

In and of themselves, **nerve** cells are able to regenerate but the central nervous system has a barrier that prevents this **regeneration**. So called neurotrophic factors allow **nerve** cells to regenerate. With the help of these factors, **nerve** cells can overcome the inhibitory barrier and regenerate.

Testing a variety of factors, the researchers were able to restore some sensation with two of the factors. These factors were infused into the cerebrospinal fluid and the rats regained sensation for pressure as well as heat.

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Until this study, many in the scientific community thought that the central nervous system's "intrinsic" barrier was insurmountable. This study demonstrated three key findings:

- From an anatomical standpoint, it is possible to grow **nerve** fibers back into the spinal cord.
- The **nerve** fibers are able to reconnect with **nerve** cells.
- The ability to "feel" can be regained.

The next phase of the study will delve into the relative amounts of the neurotrophic factors that need to be infused for optimum **nerve regeneration**. The researchers will also seek to determine if the neural pathways can be sustained over longer periods of time.

The researchers are optimistic that their findings will one day allow humans with sensory **nerve** damage to "feel" again. They also believe that "theoretically" the results could be applied to other types of nerves and perhaps even to muscle **regeneration**.

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What do you think? How close do you think this puts us to finding a cure for paralysis? What do you think are the most promising lines of research in **nerve regeneration**? Come on over to the Biology Forum and share your thoughts, opinions and feelings. Till next time...

For additional information see:

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Report from Discovery Channel Canada.

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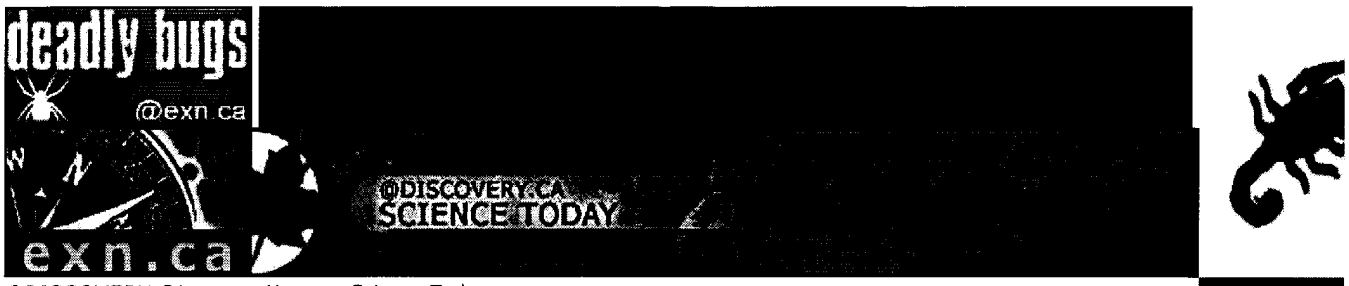

Spinal cord regeneration in humans one step closer to reality

By: Emma Reid, *January 20, 2000*

A recent breakthrough has been made in the race to find a way to regenerate neurons to help repair damage in adult spinal cords. A team of researchers, led by Canadian neuroscientist Dr. Matt Ramer at King's College London in England, has published their study in the latest issue of the journal *Nature*. It culminates a year-and-a-half-long involvement for Dr. Ramer.

Their research has managed to bridge a spinal gap that has plagued neuroscientists for some time. This gap is actually the junction between the peripheral nerves (the ones that run throughout the body) and the spinal cord itself. The brain and spinal cord send messages to the muscles through a set of nerves asking them to contract or flex, and then receives messages about our environment (heat or cold for example) through another set, the sensory nerves. When these sensory nerves are damaged, mostly through injury, they will not grow back into the spinal cord. The information loop is therefore broken and any feeling is permanently lost.

What Dr. Ramer and his colleagues have managed to do is find a way to regrow the sensory **nerve** fibres back

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into the spinal cord in rats. The implication of these experiments for humans is that patients with sensory **nerve** injuries may be able to 'feel' once again.

The team demonstrated three important factors in determining whether the nerves had truly re-established themselves structurally and functionally. First they showed that it is possible, anatomically, to grow **nerve** fibres back into the spinal cord. Second, they measured an electronic impulse showing these **nerve** fibres are actually reconnecting with **nerve** cells. Finally, they showed that the ability to feel had again been achieved.

These three conditions had historically been thwarted by what, until recently, had been perceived as the intrinsic barrier of the central nervous system.

"If we can get these sensory neurons to overcome this inhibitory barrier that is provided by the central nervous system, then hopefully we can use the knowledge and some of the neurotrophic factors to get other neurons to grow," says Ramer. The neurotrophic factors Ramer refers to are the key ingredients allowing the **nerve** cells to regenerate in the first place.

Neurotrophic factors are needed to overcome the prohibitive mechanisms of the central nervous system. **Nerve** cells have the innate ability to regenerate, but can't beat the barrier that the central nervous system already has. The neurotrophic factors give the **nerve** cells the extra power to overcome those odds. They are small protein molecules that are important in **nerve** growth development and guidance. There have been close to 50 different growth factors isolated so far, and different growth factors have different effects on different types of **nerve** cells (such as cells specific to touch, heat, pressure, or body position to name a few).

Ramer and his team ran tests using different growth factors and they infused these into the cerebrospinal fluid (which bathes the spinal fluid). They did this after crushing the area where the dorsal root enters the spinal cord of rats. They tested four different types of growth factor and used a variety of stimulus-response reactions in the rats. Two of the growth factors allowed the rats to recover feeling sensations - such as heat and strong pressure.

Ramer is excited about what these findings suggest in principle. His team has demonstrated that it is possible to overcome gaps for the sensory neurons using the growth factors, and is optimistic it can happen elsewhere. "In principle we have shown it is possible for sensory neurons to regenerate," says Ramer. "That can hopefully be applied throughout the nervous system in other neurons like motor neurons, or neurons from the brain down to the spinal cord, and from there out to the muscles, to regenerate."

Ramer and his team are setting their sights on the next phase of research. They have not determined whether it is possible to re-establish neural links after a substantial time period, like weeks or months. The team also has to determine what optimal combination of the growth factors is needed to regrow the right amount of cells, and whether or not it would be a one-off treatment or be administered over a long period of time. Ramer is confident they will be able to answer these questions in his lab.

"While a precise estimate is tricky, we would estimate that the time scale for clinical application is on the order of years rather than decades," he says.

June 24, 2004

Human Trials of Canine Paralysis Treatment to Begin

By Brian Carnell

Tuesday, December 26, 2000

Human trials will begin shortly on an implantable device that successfully promoted **nerve** regrowth in dogs and may be able to increase **nerve regeneration** in people who suffer from some forms of spinal cord injury.

In experiments with dogs, the device stimulated regrowth of **nerve** cells if the device was implanted within two weeks after certain spinal cord injuries. The device emits a very weak electrical field of about 600 microvolts per millimeter which mimics the electrical field present during rapid **nerve** growth in **human**

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and **animal** embryos.

In canine trials, about 85 percent of the injured animals showed improvements in bodily functions, including a few who regained the ability to walk after being paralyzed. Whether or not such results will translate to **human** beings remains to be seen.

"Something will happen," neurosurgeon Scott Shapiro told the Associated Press. "The question is how robust the response will be. We'll just have to wait and see."

As Naomi Kleitman, education director for the Miami Project to Cure Paralysis, told the Associated Press,

> The fact that they're going to a clinical trial in Indianapolis is very exciting and it's good evidence that the field has made progress, but obviously we have to be realistic. There's no guarantee any of this will work in humans.

But, of course, it is important to go ahead and try, regardless of the outcome.

Source:

Trials begin for paralysis patients. Rick Callahan, The Associated Press, December 10, 2000.

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1: Physiol Rev. 1996 Apr;76(2):319-70.

Degeneration and regeneration of axons in the lesioned spinal cord.

Schwab ME, Bartholdi D.

Brain Research Institute, University of Zurich, Switzerland.

For many decades, the inability of lesioned central neurons to regrow was accepted almost as a "law of nature", and on the clinical level, spinal cord and brain lesions were seen as being irreversible. Today we are starting to understand the mechanisms of neuronal regeneration in the central nervous system and its presence in the periphery. There is now a rapid expansion in this field of neuroscience. Developmental neurobiology has produced tools and concepts that start to show their impact on regeneration research. This is particularly true for the availability of antibodies and factors and for the rapidly growing cellular and molecular understanding of crucial aspects of neurite growth, guidance, target finding, and synapse stabilization. New cell biological concepts on the mechanisms of neuron survival and death and on the interaction of inflammatory cells with the central nervous system also find their way into the field of spinal cord and brain lesions and have, indeed, led already to new therapeutic approaches. This review briefly summarizes the current knowledge on the mechanisms involved in degeneration and tissue loss and in axonal regeneration subsequent to spinal cord lesions, particularly in mammals and humans.

Publication Types:
- Review
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Jun 7 2004 18:11:57

Human cells patch up rat spinal cord

Cell transplants pave the way for **human** testing of multiple sclerosis therapy.

23 February 2001

CORIE LOK

Cells from **human nerve** tissue, when transplanted into rats, can repair damaged spinal cords and restore **nerve** impulse activity, scientists report[1]. Their results open the door to possible therapies for the degenerative **nerve** disease multiple sclerosis (MS) and even paralysis.

To carry electrical impulses quickly through the body, **nerve**

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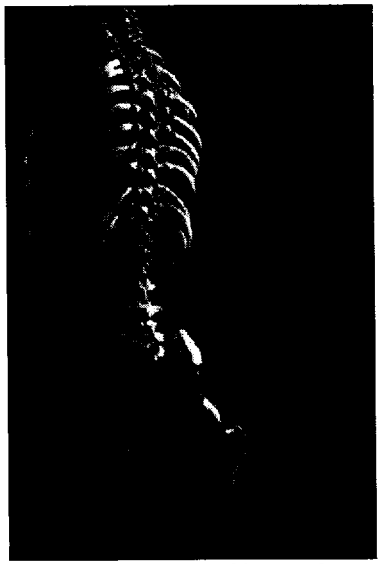
fibres must be coated with Schwann cells, which form a layer called a myelin sheath around the fibre. Although scientists do not know the exact cause of MS, in MS patients the myelin sheath in the brain and spinal cord gradually withers away and **nerve** impulses move sluggishly, or not at all. Symptoms of the disease range from numbness and loss of balance to paralysis.

As a model for MS, Ikuhide Kohama and his team from Yale University in Connecticut used rats with their spinal cords partially stripped of myelin. They removed Schwann cells from amputated **human** limbs and froze and stored them. The cells were then thawed and transplanted into the rats' spinal cord. To prevent them from rejecting the **human** cells, the animals' immune systems were suppressed with drugs.



Transplanted cells could open the door to spinal cord therapy.

The researchers found that not only did the grafted cells grow and fill in the gaps in the myelin sheath, but electrical measurements revealed that **nerve** impulse conduction improved to near-normal levels along the repaired spinal cords.

"This raises the possibility that a patient's own cells may be used to treat diseases that involve the loss of myelin," says Moses Chao, a neurobiologist studying the triggers for myelin formation at the New York University School of Medicine.

But researchers do not know whether Schwann-cell transplants will repair myelin in humans in the same way as in animals. They are therefore planning clinical trials to test the safety of transplanting an MS patient's own Schwann cells into their brain. Pending approval from a Yale University **review** board, the researchers expect the trial to start at Yale in the next few months.

Kohama's experiments mark the first time that **human** Schwann cells have been preserved by freezing and transplanted into an **animal** model, according to Naomi Kleitman of the Miami Project to Cure Paralysis, based at the University of Miami in Florida. Kleitman, who works on Schwann-cell transplantation, says researchers think that preservation by freezing will be an important step in **human** transplantation.

Schwann cells are multi-talented components of the nervous system. **Animal** studies have shown that not only do they cause myelin to regrow on the spinal cord and on nerves throughout the body, but they also promote the **regeneration** of spinal cord **nerve** fibres themselves -- a crucial step in curing paralysis.

Further work will be needed to test the movement and coordination of animals and humans after Schwann-cell transplantation, to see if the new cells actually reduce the physical symptoms of MS, the authors say.

References

1. Kohama, I., Lankford, K. L., Preiningerova, J., White, F. A., Vollmer, T. L. & Kocsis, J. D. Transplantation of cryopreserved adult **human** Schwann cells enhances axonal conduction in demyelinated spinal cord. ***Journal of Neuroscience*** **21**, 944 - 950 (2001).

Current Treatment for **Human** Spinal Cord Injury

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What is the best treatment for someone who has just suffered a spinal cord injury? In a recent conversation, Wise Young, who heads the Neurosurgery Research Laboratory at New York Medical Center in New York City, listed the following steps. Young has an 18-year-old daughter and he described what he would do if she were injured.* (The following information is not to be considered as a guide for treating patients with spinal cord injuries. Instead, it is to be used only as a source of information.)

1. GIVE METHYLPREDNISOLONE

"I would move heaven and earth to make sure that she received *methylprednisolone* as soon as possible," said Young. The latest studies of the drug, which the federal Food and Drug Administration approved as an emergency treatment for spinal cord injury in 1990, show that it is best to give methylprednisolone within three hours after a spinal cord injury

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occurs. Patients can benefit from treatment later than that -- up to eight hours after the injury -- but "there's a real need to give it immediately," says Young.

Researchers do not know exactly how methylprednisolone helps injured spinal cord tissue to recover, but they speculate that the drug has at least two main effects. One is that methylprednisolone, which is a synthetic *steroid*, suppresses immune responses throughout the body. This can be beneficial for patients who have spinal cord injuries because vigorous *inflammatory responses* at the site of injury may worsen its impact.

The second way in which methylprednisolone works may be to block the formation of *free radicals*. These charged, highly energetic ions can disrupt the membranes of cells that were not initially injured. So the overall effect of methylprednisolone for people with spinal cord injuries seems to be protective: The drug apparently prevents destructive inflammatory responses at the site of injury and it also prevents the formation of free radicals.

Researchers are continuing to study the effects of methylprednisolone and to design drugs that capture its benefits without causing unwanted side effects, such as too much immune suppression throughout the body.

2. REMOVE ANY BONE THAT IS COMPRESSING THE SPINAL CORD

Next, Young would be certain that his daughter received a special operation called "surgical decompression of the spinal cord." In most people who have spinal cord injuries,the spinal cord is compressed, not cut. Thus, the rationale for using surgery to decompress the injured cord is to relieve any pressure from surrounding bone. Pressure on spinal cord tissue can cause mechanical damage as well as cutting off the supply of blood and oxygen.

But the surgery is controversial, says Young, and it is also a difficult and expensive procedure. Young recommends doing the surgery as soon as possible. But he acknowledges that "there are simply no guidelines" for neurosurgeons about when and under what circumstances they should the surgery.

3. STABILIZE THE SPINE

Young also recommends surgery to stabilize the spine. Stabilization should prevent further compression or twisting of the spinal cord and it should also

allow the injured person to be hoisted upright in a specialized bed frame as soon as possible. "The rehabilitation period is much longer if the patient remains lying down," says Young.

4. CONSIDER SCHWANN CELL IMPLANTS AS EXPERIMENTAL THERAPY

Of all the experimental treatments for spinal cord injury that researchers are investigating, Young would most seriously consider a *Schwann cell* transplant.

Schwann cells are not normally present in the central nervous system (CNS), which includes the brain and spinal cord. Instead, Schwann cells occur in the *peripheral nervous system (PNS)*, which serves the rest of the body. Their function is to produce many layers of a membranous, fatty wrapping called *myelin* that surrounds **nerve** cell *axons*, the threadlike fibers of **nerve** cell cytoplasm that conduct electrical impulses from a **nerve** cell to its target. Myelin increases the speed of **nerve** cell impulses and is necessary for the normal functioning of most **nerve** cells in the brain and spinal cord.

Researchers consider using implants Schwann cells to help repair damaged spinal cord axons because they may act as a physical bridge, supply nourishing chemical factors that encourage **regeneration**, and allow the normal functioning of undamaged or regenerated axons. In humans, the procedure would involve removing a small amount of the patient's own peripheral **nerve** tissue, isolating Schwann cells from the tissue, growing them in plastic culture dishes in an incubator, then implanting the cultured Schwann cells into the site of spinal cord injury.

The strategy of using purified Schwann cells or bits of PNS tissue to repair injured brain and spinal cord axons has emerged from many decades of research on animals. Researchers have learned that by transplanting PNS tissue into the site of an injury in the brain or spinal cord, they can sometimes induce injured CNS axons to regrow. (In fact, the Swedish investigator, Lars Olson, heads a team of researchers who recently reported using tiny bridges of PNS tissue to repair the spinal cords of adults rats.

The transplanted PNS tissue may enhance the **regeneration** of brain or spinal cord axons for several reasons. PNS tissue -- which includes Schwann cells -- contains nourishing chemical factors called *neurotrophins* that stimulate axons to regrow. Also, tissue from the peripheral nervous

system lacks inhibitory factors that are normally present in CNS tissue and that seem to prevent axon regrowth after an injury. Additionally, the noncellular material -- known as the *extracellular matrix* -- that surrounds **nerve** cells has a different chemical composition in the PNS than does the corresponding extracellular material in the CNS. All of these chemical differences -- the combinations of neurotrophins, inhibitory factors, and the composition of the extracellular matrix -- make the peripheral nervous system a more hospitable environment than the central nervous system for axonal **regeneration**.

Finally, transplanted Schwann cells should help maintain the myelin wrapping that is so essential to the normal function of **nerve** cells. "Myelin turns out to be a very major factor in spinal cord injury," says Young. Often-- a week or two after a spinal cord injury -- a wave of cell suicide occurs in the CNS cells that make myelin, which are called *oligodendrocytes*. As a result, the myelin wrapping around the axons of spinal cord **nerve** cells becomes very thin, which makes the axons incapable of transmitting **nerve** impulses fast enough to accomplish their normal functions. If another source of myelin -- from transplanted Schwann cells -- could be supplied, the intact and regenerating **nerve** cells might function more normally.

5. BEGIN REHABILITATION AS SOON AS POSSIBLE

Rehabilitation therapy for patients with spinal cord injuries takes many forms, depending on the site and extent of injury and the age and medical condition of the patient.

* There are no national guidelines for treating acute spinal cord injuries, although many emergency medical teams administer methylprednisolone and stabilize the spine. The treatments described here should not be interpreted as guidelines for medical practitioners. Rather, they are intended to inform readers about existing treatments and potential therapies that may some day be available.

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